GENETIC EPIDEMIOLOGICAL INVESTIGATIONS OF CORONARY ARTERY DISEASE AND ITS RISK FACTORS

CHANG XULING

(Bachelor of Science, Zhejiang University, China)

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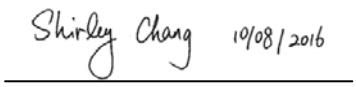
Supervisor:

Associate Professor Heng Chew Kiat

DECLARATION

I hereby declare that this thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has also not been submitted for any degree in any university previously.



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Summary

This dissertation is focused on the genetic epidemiological investigations of coronary artery disease (CAD) and its related risk factor traits.

With the rapid development of genome-wide association study (GWAS), many single nucleotide polymorphisms (SNPs) have been reported to be associated with CAD and its related traits. Rs6903956 on androgen-dependent tissue factor pathway inhibitor (*TFPI*) regulating protein (*ADTRP*) gene was identified to associate with CAD in a GWAS conducted in a Han Chinese population. The association has been replicated in the Singaporean Chinese and we investigated whether the genetic variant in the *ADTRP* gene was associated with plasma coagulation factors, Factor VII (FVII) and fibrinogen in the Singaporean Chinese.

The identification of many other SNPs associated with CAD and its related traits by GWAS also provides a chance to evaluate whether the inclusion of genetic variants into phenotypic based risk prediction models, such as the Adult Treatment Panel III (ATPIII) model from the Framingham Heart Study (FHS) could improve risk prediction accuracy and performances. We utilized SNPs from GWAS catalog to construct various forms of Genetic Risk Score (GRS) for augmenting the ATPIII model. C-statistics and net reclassification improvement (NRI) index were used to evaluate the performance of the new models.

As with all complex traits, it is known that gene-gene and gene-environment interactions also play a role in determining the outcome of CAD and its related risk factors. The last component of the dissertation included gene-diet interaction study for body mass index (BMI) and gene-gene interaction study for plasma lipid levels.

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List of Abbreviations

Activated form of FVII (FVIIa)

Activated form of factor X (FXa)

Activating transcription factor 3 (ATF3)

Adult Treatment Panel III (ATPIII)

Analysis of variance (ANOVA)

Androgen-dependent *TFPI* regulating protein (*ADTRP*)

Angiotensin converting enzyme (*ACE*)

Apolipoprotein A5 (*APOA5*)

Apolipoprotein B (apoB)

Apolipoprotein E (apoE)

Arteriosclerotic vascular disease (ASVD)

ATP-binding cassette, subfamily a, member 1 (*ABCA1*)

Base pairs (bp)

Blood pressure (BP)

Body mass index (BMI)

C-reactive protein (CRP)

Cardiovascular disease (CVD)

C-C motif chemokine receptor 2 (CCR2)

CCCTC-binding factor (CTCF)

Cholesteryl ester transfer protein (*CETP*)

Chorionic somatomammotropin hormone 1 (CS-1)

Chromosome 6 open reading frame 106 (*C6orf106*)

Coagulant activity (FVIIc)

Coefficient of variation (CV)

Coiled-coil domain containing 171 (*CCDC171*)

Confidence Interval (Cl)

Coronary artery disease (CAD)

Coronary heart disease (CHD)

Cyclin-dependent kinase 2A (*CDKN2A*)

Cyclin-dependent kinase 2B (*CDKN2B*)

Diastolic blood pressure (DBP)

Dynamin 2 (*DNM2*)

E1A binding protein p300 (EP300)

Electrocardiography (ECG-LVH)

Endothelial cell (EC)

ETS proto-oncogene 1, transcription factor (ETS1)

Factor VII (FVII)

Factor IX (FIX)

Factor X (FX)

Familywise error rate (FWER)

False discovery rate (FDR)

Fat mass and obesity-associated protein (*FTO*)

Fifth Joint National Committee on Hypertension (JNC-V)

Food-frequency questionnaire (FFQ)

Forkhead box P1 (FOXP1)

Framingham Heart Study (FHS)

GATA binding protein 3 (GATA3)

Genetic Risk Score (GRS)

Genome-wide association studies (GWAS)

GLI family zinc finger 1 (GLI1)

Glucokinase regulatory protein (*GCKR*)

Han Chinese from Beijing (CHB)

'Hard' coronary heart disease ('hard' CHD)

Hardy–Weinberg expectation (HWE)

Heart and neural crest derivatives expressed 1 (*HAND1*)

Hemoglobin A1c (HbA1c)

Hepatocyte nuclear factor-1α (*HNF1A*)

High-density lipoprotein (HDL)

High-sensitive C-reactive protein (hsCRP)

Histone deacetylase (*HDAC*)

Histone deacetylase 2 (HDAC2)

Human vascular endothelium cells (HUVEC)

Identity by descent (IBD)

Institutional Review Boards (IRB)

Integrin alpha 4 beta 1 (Very Late Antigen-4, VLA-4)

Interferon gamma (*IFNγ*)

Ischemic heart disease (IHD)

Japanese in Tokyo (JPT)

Jun proto-oncogene, AP-1transcription factor subunit (AP-1)

Leave-one-out (LOO)

Linkage disequilibrium (LD)

Low-density lipoprotein (LDL)

Melanocortin 4 receptor (*MC4R*)

Methylthioadenosine phosphorylase (MTAP)

Minor allele frequency (MAF)

Minute (min)

Monocyte chemotactic protein (MCP-1)

Monounsaturated fatty acid (MFA)

MYB proto-oncogene, transcription factor (MYB)

Myocardial infarction (MI)

Myogenic factor (MYF)

Myogenic differentiation 1 (MYOD1)

National Center for Biotechnology Information (NCBI)

National Cholesterol Education Program, Adult Treatment Panel II (NCEP ATP II)

National University of Singapore (NUS)

Nested case-control (NCC)

Net reclassification improvement (NRI)

Nitric oxide (NO)

Non-coding RNA (ncRNA)

Noncommunicable disease (NCD)

Peroxisome proliferator-activated receptor (PPAR),

Peroxisome proliferator-activated receptor-γ (PPAR-γ)

Polyunsaturated fatty acid (PFA)

Potassium two pore domain channel subfamily K member 3 (*KCNK3*)

Proline and serine rich coiled-coil 1 (*PSRC1*)

Prothrombin time (PT)

Quality control (QC)

RAD21 cohesin complex component (RAD21)

Restriction fragment length polymorphism (RFLP)

Retinoic acid receptor beta (*RARB*)

Reverse cholesterol transport (RCT)

Saturated fatty acid (SFA)

Singapore Chinese Eye Study (SCES)

Singapore Chinese Health Study (SCHS)

Singapore Indian Eye Study (Sindi)

Singapore Malay Eye Study (SiMES)

Singapore Myocardial Infarction Registry (SMIR)

Singapore Prospective Study Program (SP2)

Single nucleotide polymorphism (SNP)

SIX homeobox 5 (SIX5)

Smooth muscle cell (SMC)

Standard error (SE)

Standard deviation (SD)

Sterol O-acyltransferase 1 (SOAT1)

Structural maintenance of chromosomes 3 (SMC3)

Systolic blood pressure (SBP)

T-box 5 (*TBX5*)

TGFB induced factor homeobox 1 (TGIF1)

Tissue factor (TF)

Tissue factor-factor VIIa (TF-FVIIa)

Tissue factor pathway inhibitor (*TFPI*)

Total cholesterol (TC)

Transcription factor 7 like 2 (*TCF7L2*)

Triglycerides (TG)

University of Minnesota (UMN)

Upstream binding protein 1 (LBP-1)

Upstream stimulatory factor (*USF1*)

Vascular cell adhesion molecule 1 (VCAM-1)

Weighted Genetic Risk Score (wGRS)

White blood cell (WBC)

World Health Organization (WHO)

Zic family member 1 (Zic1)

Chapter 1: Introduction

1.1 Coronary artery disease

Coronary heart disease (CHD), also widely known as ischemic heart disease (IHD) [1] or coronary artery disease (CAD) is the most common type of cardiovascular disease (CVD) [2]. The essential mechanism of CAD involves atherosclerosis of the heart arteries [3]. Atherosclerosis is a phenomenon that the artery walls become thick due to the accumulation of white blood cells (foam cells) and fatty acids inside the blood vessel walls. Fibrofatty plaques will form at the accumulation areas. The development of plaques will reduce the elasticity of the artery walls, gradually affect blood flow and eventually lead to increased pulse pressure. The progression of CAD will last for decades [4]. Patients will usually be asymptomatic and not aware of their disease status until a sudden heart attack finally arises.

Myocardial infarction (MI), commonly known as heart attack, is the most severe complication for CAD. CAD and MI are leading causes of mortality and morbidity worldwide [5]. It accounted for 8.14 million global deaths (16.8%) in 2013, the number of which had rose rapidly since 1990 (5.74 million deaths) [2]. CAD may influence individuals at any age groups but will be more common in older age groups [6] and in males [7]. According to world health statistics in 2012 [8], the largest proportion of non-communicable disease (NCD) deaths is attributed to CVD (48.0%), and it is estimated that the annual death caused by CVD will increase to 25 million in 2030. Although the mortality and morbidity rate of CAD has decreased from 1980

to 2010 in developed countries due to improved prevention and treatment [9, 10], it increased rapidly in developing countries. In Asia, there is an increasing CAD burden due to rising prevalence of sedentary lifestyle and changes in food consumption [11, 12]. Although South Asian only accounts for 20% of the world's population, 60% of the world's CVD burden is estimated to occur in Asia. In Singapore, CAD is the No.3 killer only after cancer and pneumonia (https://www.moh.gov.sg/content/moh_web/home/statistics/Health_Facts_Singapore/Principal_Causes_of_Death.html). Therefore, it is essential to investigate the epidemiology of CAD to reduce the disease burden both on the health systems and individuals in Asia.

CAD is a complex disease. Both genetic and lifestyle factors, as well as their interactions contribute to the etiology of CAD. Many environmental and lifestyle factors promote the progression of CAD. These risk factors include behavioural risk factors (unhealthy diet, lack of physical activity, excessive alcohol intake and tobacco use), metabolic risk factors (high blood pressure, diabetes, elevated blood cholesterol, overweight and obesity) and some other risk factors such as depression [3]. Cigarette smoking is the strongest environmental risk factor of CAD, which accounts for about 36% of cases [13]. Obesity is associated with 20% [13] of CAD cases and physical inactivity was shown to associate with 7-12% of cases [14]. Interventional studies showed that some risk factors could be modified to reduce the mortality and morbidity of CAD, especially behavioural risk factors [15-17]. Thus further studies

to investigate the casual relationship between risk factors and CAD and possible mechanisms involved are needed.

Besides lifestyle factors, genetic variations are likely to have a prominent role in the etiology of CAD as the heritability of CAD is estimated to be up to 60% [18-20]. Previously, many genes involved in metabolic pathways related to CAD have been identified through candidate gene approach, such as ATP-binding cassette, subfamily a, member 1 (*ABCA1*) in lipid metabolic pathway and angiotensin converting enzyme (*ACE*) in the blood pressure regulation [21, 22]. In recent years, the advances of large scale genome-wide association studies (GWAS) have made it possible to assess many single nucleotide polymorphisms (SNPs) across the genome and uncovered SNPs that are associated with CAD and its related risk factor traits. The rapid development and the reduction in the cost made GWAS a powerful tool to provide a valuable first insight into candidate loci or genetic architecture of CAD for subsequent validation and biological analysis [23].

1.2 Coronary artery disease related traits

1.2.1 Obesity and body mass index

The body mass index (BMI) or Quetelet index is a simple index to quantify the amount of tissue mass in an individual. It is calculated as weight in kilograms (kg) divided by height in meter square (m^2) thus is universally expressed in the unit of kg/m^2. Based on the value of BMI, the World Health Organization (WHO) defines

overweight as the value of BMI greater than or equal to 25 kg/m^2 and obesity as the value of BMI greater than or equal to 30 kg/m^2 [24]. Some Asian countries including Singapore use lower BMI values as cut-off for overweight (BMI $\geq$ 23 kg/m^2) and obesity (BMI $\geq$ 27.5 kg/m^2) [25] since there are several studies shown that compared with Caucasians at the same BMI level, Asians have higher proportion of body fat and higher risk for several diseases [26-28]. Overweight and obesity, which are defined as the abnormal or excessive accumulation of fat, are major health problems worldwide. A total of 2.8 million people die each year due to being overweight or obese worldwide [29] according to world health statistics in 2012 [8]. The mortality rate was higher in individuals who were overweight and obese than those were underweight [24]. The worldwide prevalence of obesity has been more than two times higher since 1980. In 2014, more than 1.9 billion adults (18 years and above) were overweight (39%) and over 600 million of these individuals were obese (13%). Women were more likely to be overweight (40% Vs 38%) and obese (15% Vs 11%) than men [24]. In Singapore, obesity places the 4th heaviest disease burden on the whole society after hypertension, diabetes and high total cholesterol. Between 1998 and 2004, the prevalence of obesity among Singaporean adults aged 18 to 69 years old increased slowly from 6.0% to 6.9% while the prevalence increased rapidly and jumped to 10.8% only after 6 years in 2010 (https://www.moh.gov.sg/content/moh_web/home/statistics/Health_Facts_Singapore/Disease_Burden.html). Being overweight or obese will lead to deleterious metabolic effects on lipid levels and blood pressure. In addition, individuals who

are overweight or obese will have higher risk for various diseases, such as type 2 diabetes, CHD, ischaemic stroke, obstructive sleep apnea, musculoskeletal disorders and certain types of cancers [8, 30].

Obesity is a complex disease, which is associated with both environmental factors, such as dietary intake and physical inactivity, and genetic components as well as their interactions [31-33]. Overweight and obesity are mainly attributed to an energy imbalance between calories intake (diet) and expenditure (physical activity). There has been a global increase of energy-dense western style food intake and decrease in amount of physical activity due to sedentary lifestyle [34]. Overweight and obesity are mostly preventable if making the right choice of food and engaging in regular exercise. Besides lifestyle factors, genetic factors also play an essential part in the progression of obesity. Among all the genes reported, fat mass and obesity-associated protein (*FTO*) is the most valid and with the largest effect size on obesity risk [35]. In addition to environmental and genetic factors acting independently, it is suggested that the association between genes and overweight/obesity could be modified by dietary intake [36-39]. Thus investigating the gene-diet interaction for obesity might uncover the mechanisms involved and provide additional guidance to reduce the prevalence of overweight and obesity.

1.2.2 High density lipoprotein

High-density lipoprotein (HDL) is the smallest and densest lipoprotein particles with

the protein to lipids proportion being highest among the five major lipoprotein groups. Lipoproteins are complex particles which are responsible for lipids transportation around the body within the bloodstream. Usually larger lipoprotein will transport fat molecules such as cholesterol, phospholipids and triglycerides (TG) to cells while HDL is just the opposite that it removes fat from cells. The fat removed is mostly delivered by HDL through both direct and indirect pathways to the liver and steroidogenic organs and is excreted into the bile and transformed into bile acids. HDL is sometimes regarded as "good cholesterol" since it can remove fat molecules out of artery walls. The removal of fat could help to reduce macrophage accumulation and thus prevent or even regress atherosclerosis. The most classical pathway indicating the protective function of HDL toward atherosclerosis is the reverse cholesterol transport (RCT). HDL plays a central role in RCT, a multi-step process that transports cholesterol from the peripheral tissues, for instance foam cells and macrophages, to the liver for excretion into the bile via plasma. Low concentration of HDL level (men < 40 mg/dL and women < 50 mg/dL) is strongly associated with accumulation of plaques within the arteries walls and will eventually lead to increased risk of stroke, sudden plaque ruptures, cardiovascular disease and vascular disease [40, 41]. Every 1 mg/dl decrease in HDL level will lead to a 6% increase in cardiovascular risk [42].

Cholesterol ratio is the ratio between HDL and total cholesterol level in the plasma. In the last decade, some researchers believe that lipoprotein ratios would be much

more important than the absolute lipoprotein levels in some aspects, such as risk prediction for heart disease [43]. Thus cholesterol ratio has become another important area of interest in addition to absolute levels of HDL, TG, total cholesterol (TC) and low-density lipoprotein (LDL).

High concentration of HDL level (> 60 mg/dL) has a protective effect against vascular disease. The level of HDL tends to be higher in women than in men, both in size and the cholesterol content. In addition, many lifestyle factors could affect HDL levels. Moderate alcohol intake could increase HDL levels and lower risk and all-cause mortality rate of cardiovascular disease [44]. Changes in the exercise and dietary habits, such as increase the amount of soluble fiber intake and decrease carbohydrate intake, also have a positive effect of elevating HDL level. In addition, increasing the strength of aerobic exercise and keep normal weight could also help with raising the HDL levels. Identifying more elements that could affect HDL levels and investigating the possible mechanisms involved is important in the diagnosis, treatment and prevention of heart disease [45].

1.3 Objectives and aims

1.3.1 Study I - The genetic variation rs6903956 in the novel *ADTRP* gene is not associated with levels of plasma coagulation factors in the Singaporean Chinese (Chapter 4)

GWAS has reported that rs6903956 within the first intron of androgen-dependent

tissue factor pathway inhibitor (*TFPI*) regulating protein (*ADTRP*) gene was associated with CAD risk in the Han Chinese population [46]. The association has been replicated in several independent Chinese cohorts, including our Singaporean Chinese [47] and Japanese but with different risk allele in the Japanese [48]. However, the mechanism involved is largely unknown. Previously it was reported that the association was not explained by lipid levels [47]. Factor VII (FVII) and fibrinogen are the key factors in coagulation cascade and independent risk predictors for CAD [49-52]. The aim of this study was to investigate whether there is any association between the genetic variant on *ADTRP* and plasma coagulation factors, FVII and fibrinogen levels, in the Singapore Chinese population.

1.3.2 Study II - Utility of genetic and non-genetic risk factors in predicting Coronary Heart Disease in Singaporean Chinese (Chapter 5)

In recent years, numerous phenotype based equations for predicting risk of 'hard' coronary heart disease ('hard' CHD), which includes myocardial infarction and coronary death, are available. The most frequently used model among them is the Framingham Risk Equation, which includes major CHD risk factors, such as age, HDL, TC, systolic blood pressure (SBP), current smoking status and use of anti-hypertensive medication. Although the original phenotype-based risk prediction model performed well in multiple cohorts with or without model recalibration, there are still a large number of individuals with few risk factors and predicted to be at low risk of developing disease were actually CHD patients. Some

studies tried to include other phenotypic risk predictors, such as biomarker high-sensitive C-reactive protein (hsCRP) and creatinine, into the risk prediction model, but the improvement was limited [53-55]. Besides lifestyle factors, genetic information are likely to have a prominent role in the etiology of CHD. However, limited data exists regarding the utility of genetic information for risk prediction in Chinese populations. The aim of the study was to evaluate whether genetic factors could improve prediction accuracy of incident 'hard' CHD in a Chinese population, beyond the use of traditional risk factors and biomarkers.

1.3.3 Study III - Interactions between genes and dietary intake and their effect on body mass index in the Singaporean Chinese population (Chapter 6)

Recent GWAS have identified 97 BMI associated SNPs. These obesity risk SNPs are generally transferable between ethnic groups, for which similar associations have been reported. Differences however, exist in dietary patterns between ethnic groups and whether dietary intake of various nutrients can modify obesity associations at these recently identified risk loci, especially in the Asian population, is not well understood. The aims of this study were to investigate:

(1) The association between dietary components and BMI;

(2) The association between BMI associated risk loci / weighted Genetic Risk Score (wGRS) and BMI in Singapore Chinese cohorts;

(3) The association between BMI associated risk loci / wGRS and various dietary

components intake;

(4) Interaction between known index variants at obesity risk loci and intake of various dietary components for BMI in the Singaporean Chinese population.

1.3.4 Study IV - Interactions between high-density lipoprotein associated risk loci and SNPs across the genome on high-density lipoprotein levels and cholesterol ratio in Singaporean Chinese (Chapter 7)

Plasma HDL level is strongly associated with accumulation of atherosclerosis within the arteries walls and risk of vascular disease. Large scale GWAS have identified many SNPs associated with blood HDL levels. However, the SNPs uncovered thus far only explained a very small fraction of HDL variation. One possible explanation for the 'missing heritability' is the gene-gene interaction. The aim of this study was to investigate the interactions between HDL associated risk loci from GWAS catalog and independent SNPs across the genome for HDL levels and cholesterol ratio in Singaporean Chinese cohorts thus to extend the understanding of the genetic basis of HDL and to improve the diagnosis, treatment and prevention of heart disease.

Chapter 2: Literature Review

This chapter summarizes the literature pertinent to the epidemiological investigation of CAD and its related risk factor traits. We first reviewed the pathology of CAD, followed by GWAS, the most powerful tool to date for studying genetic basis of the complex diseases. The development of the well-known cardiovascular cohort study, Framingham Heart Study (FHS) and the CHD risk perdition models derived from FHS will be reviewed thereafter. Lastly, gene-gene and gene-environment interaction studies for CAD and its related traits will also be surveyed.

2.1 Pathology of coronary artery disease

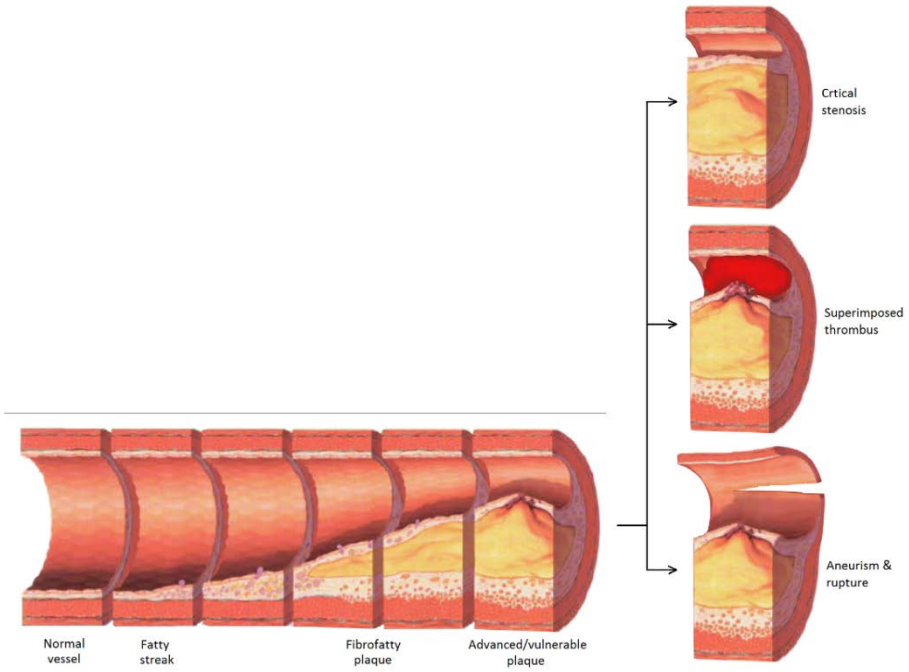
Atherosclerosis, also known as arteriosclerotic vascular disease (ASVD), is a progressive disease characterized by thickening of artery walls due to invasion and accumulation of foam cells (white blood cells), lipids and fibrous elements. The accumulations of white blood cells (WBCs) are named ‘fatty streaks’ because of the similar appearance with marbled steak and they contain both living and dead cells as well as lipids. In humans, the ‘fatty streaks’ begin in the first decade of life in the aorta, then during the second decade in the coronary arteries, followed by the cerebral arteries during the third or fourth decades [56]. Different regions of arteries have different probability for lesion formation. The branch and curvature parts of the arteries are preferred sites for formation of lesions. The ‘fatty streaks’ will reduce the flexibility of the artery walls but they are only the precursors of more advanced lesions (fibrous lesions). They are not clinically significant and will not affect the

flow of blood for decades. The advanced lesions are a result of accumulation of necrotic debris which are rich in lipids and smooth muscle cells (SMCs) and are usually with a 'fibrous cap' made up by SMCs and extracellular matrix. The calcification and ulceration at the luminal surface will make the lesions more complex. Rupture or erosion of the lesion will cause the formation of thrombus or blood clot, leading to stroke (in the cerebral arteries) or myocardial infarction (in the coronary arteries).

Atherosclerosis is a chronic disease, which influences blood vessels as a result of long term inflammatory response of WBCs. The process can be promoted by high level of LDL which carry cholesterol and triglycerides and low level of functional HDL, which removes fats and cholesterol from the macrophages.

A normal artery contains three morphologically distinct layers, intima, media and adventitia. The intima is the innermost layer bounded by endothelial cells (ECs) and elastic fibers. The middle layer media is made up by SMCs and the outermost adventitia is full of connective tissues as well as small amount of fibroblasts and SMCs. The development of atherosclerotic plaques can be divided into several stages, lesion initiation, inflammation, foam cell formation, fibrous plaques and advanced lesions and thrombosis [56] (Figure 1).

Figure 1: Progression of atherosclerosis to late complications (Npatchett, 27 March 2015).



(https://en.wikipedia.org/wiki/Atherosclerosis)

2.1.1 Lesion initiation

As mentioned above, the intima and media layer are separated by a monolayer of ECs. It is a selectively permeable barrier between blood and tissues and generates molecules to regulate various biological processes, such as preventing the irregular migration and proliferation of SMCs and thrombosis [57].

When the level of circulating LDL increases in the blood, the accumulation will be promoted in the subendothelial matrix, which initializes atherosclerosis. The invasion and retention of LDL in the artery walls are influenced by the interaction between apolipoprotein B (apoB) and matrix proteoglycans [58]. Besides LDL,

other lipoproteins containing apoB could also accumulate in the artery and lead to atherosclerosis [59]. Previous studies showed that only the trapped LDL undergoing modification, such as oxidation, the most significant for lesion formation at early stage, other than native LDL will be taken up by macrophages and promote inflammation as well as foam-cell formation [60]. Functional HDL can remove excess cholesterol from peripheral tissues and inhibit oxidation of lipoprotein. Thus HDL has a protective effect on atherosclerosis.

2.1.2 Inflammation

The accumulation of modified LDL motivates the ECs to produce large amount of proinflammatory elements including growth factors and adhesion molecules. These elements will trigger the recruitment of monocytes and lymphocytes in the artery walls and promote atherosclerosis. The fabrication of anti-atherogenic mediator, nitric oxide (NO) could also be reduced by LDL [61]. Besides modified LDL, haemodynamic forces, level of homocysteine, sex hormones, diabetes and infection could also modulate and promote inflammation [62].

The binding of monocytes to the ECs is crucial for atherosclerosis and mediated by both adhesion molecules and chemotactic factors. The adhesion molecule, selectins promotes the early adhesion of leukocytes with the endothelial surface [63]. The integrin alpha 4 beta 1 (Very Late Antigen-4, VLA-4) interacts with both vascular cell adhesion molecule 1 (VCAM-1) and the chorionic somatomammotropin hormone

1 (CS-1) to contribute to the firm adhesion of monocytes and T cells to endothelium [64]. It is also found that monocyte chemotactic protein (MCP-1) and its receptor C-C motif chemokine receptor 2 (CCR2) could significantly induce atherosclerotic lesions formation and development by promoting recruitment of monocytes [65].

2.1.3 Foam cell formation

Only the highly oxidized (extensively modified) LDL particles can be absorbed rapidly and sufficiently by macrophages to form foam cells. A number of enzymes are involved in the modification of LDL to form atherosclerotic lesions (phospholipase, sphingomyelinase and myeloperoxidase). Phospholipase can induce oxidation of LDL [66]. Sphingomyelinase can promote aggregation, retention and enhanced uptake by macrophages of lipoprotein [67]. Finally, myeloperoxidase generates hypochlorous acid and tyrosyl radical and promotes modified LDL binding to macrophage scavenger receptors [68]. Two scavenger receptors, CD36 and SR-A could mediate the uptake of extensively modified LDL by macrophages to form foam cells [69, 70]. Cytokines and peroxisome proliferator-activated receptor-γ (PPAR-γ) regulate scavenger receptors expression [71]. Apolipoprotein E (apoE) secreted by macrophages could reduce the transformation of macrophages to foam cells by promoting cholesterol efflux to HDL thus it has a protective effect on atherosclerosis.

2.1.4 Fibrous plaques

Fibrous plaques contain a rising accumulation of extracellular lipid as well as SMCs

and extracellular matrix derived from SMCs. The migration and proliferation of SMCs and production of extracellular matrix are influenced by growth factors and cytokines secreted by T cells and macrophages. It is also found that the interaction between CD40 and its ligand CD40L (CD154) plays an important role in the development of advanced lesions [72]. The interaction leads to the production of several inflammatory cytokines. Many risk factors promote the development of fibrous lesions, such as hormones, high blood pressure and elevated homocysteine levels. Oestrogen could influence plasma lipoprotein levels and stimulate production of prostacyclin and NO thus it is anti-atherogenic [73]. Infection by cytomegalovirus will induce arterial restenosis and atherosclerosis [74].

2.1.5 Advanced lesions and thrombosis

It is suggested that an acute occlusion due to rupture or erosion of the lesion other than the growth and development of advanced lesions leads to acute coronary events. Rupture usually occurs at the edge of vulnerable lesions, which contain increased numbers of foam cells. Many factors contribute to the stability of atherosclerotic lesions such as calcification and neovascularization as well as the expression of some molecules which can mediate thrombosis.

2.2 Genome-wide association study

GWAS is an examination of many SNPs in different individuals to see if any SNP is associated with a diseases trait from the DNA of participants. Genotypes of

different individuals that were either with (cases) or without (controls) a disease or with different degree of phenotypes for a particular trait such as HDL levels were compared. This approach investigates the whole genome thus it is non-hypothesis driven compared to a candidate gene approach. It is under the assumption that common genetic variation plays a central part in explaining the heritability of common diseases [75]. In addition, GWAS shows superiority for investigating complex and common diseases compared to linkage studies [76]. However, researchers should still take note that GWAS has some limitations such as requiring generally a large sample size to attain adequate statistical power after correcting for multiple testing. The first GWAS was published successfully in 2005 with age-related macular degeneration as outcome [77]. To date, hundreds of human diseases and traits have been investigated by GWAS and thousands of SNPs have been identified. Raw GWAS data should undergo important quality control steps to eliminate as much spurious findings as possible. In the following sections, GWAS of CAD and its related traits will first be reviewed, followed by some key components for GWAS, including genotype calling, quality control, linkage disequilibrium, imputation, meta-analysis and multiple testing.

2.2.1 GWAS of CAD

To date, GWAS have identified 144 SNPs from 97 different risk loci that are associated with CAD / CHD / MI / MI early onset [78]. Most of the association have been replicated in independent cohorts, indicating the robustness of the results.

Detailed information of the association results are presented in Table 1 [78].

Among the 144 SNPs reported in CAD GWAS, 95 of them (65.97%) are within or near protein-coding genes and 14 of them are known to be functional. The most well-replicated and strongest associations were found between SNPs from 9p21.3 and CAD. The associations between this locus with both CAD and MI were first reported in Caucasians in 2007 [79-81]. In addition, they have been replicated in Asian population, including Koreans [82], Japanese [83] and Han Chinese [84] but not in African-Americans [85]. The associations are independent of any known CAD risk factors and the genetic variants from 9p21.3 were associated with an increased 18%-47% risk of CAD. However, the mechanism involved is largely unknown since this region is a gene desert and is not known to have any genes coding for proteins. However, the region was found to be overlapped with an annotated non-coding RNA (ncRNA), named *ANRIL* [86]. The length of *ANRIL* is 126.3 kb and its 5'UTR overlapped with cyclin-dependent kinase 2B (*CDKN2B*). *CDKN2B* and cyclin-dependent kinase 2A (*CDKN2A*) are the nearest genes to this region. Some studies showed that the genetic variation in 9p21.3 has an effect on the expression of *CDKN2A/B* in vascular SMCs and can affect the proliferation of vascular SMCs, which plays a key role in the pathogenesis of atherosclerosis [87]. Another functional study showed that 9p21.3 may promote atherosclerosis by regulating *ANRIL* expression in primary aortic SMCs. The association can thus alter gene expression that controls cellular proliferation pathway [88]. It is also reported

Table 1: Main GWAS findings for CAD / CHD / MI / MI early onset

	SNPs	Region	Disease/Trait	Sample Size	Mapped gene	Risk Allele	Context	p	OR or beta	Reference
1	rs12740374	1p13.3	CHD	8,090 / 8,849	*CELSR2*	T	UTR-3	9.00E-29	0.18	[85]
2	rs599839	1p13.3	CHD	4,864 / 2,519	*PSRC1*	A	nearGene-3	4.00E-09	1.29	[81]
				86,995 / 56,682		A		3.00E-10	1.11	[89]
3	rs602633	1p13.3	CAD	109,124	*CELSR2 - PSRC1*	T		1.00E-08	1.11	[90]
4	rs646776	1p13.3	MI (early onset)	6,042 / 19,492	*CELSR2*	T	nearGene-3	8.00E-12	1.19	[91]
			CHD	30,482 / 40,593		T		6.00E-10	1.14	[92]
5	rs17114036	1p32.2	CHD	86,995 / 56,682	*PPAP2B*	A	intron	4.00E-19	1.17	[89]
			CAD	109,124		G		1.00E-08	1.15	[90]
6	rs17114046	1p32.2	CHD	30,482 / 40,593	*PPAP2B*	?	intron	2.00E-07	NR	[92]
			CHD	30,482 / 40,593		?		3.00E-07	NR	[93]
7	rs11206510	1p32.3	MI (early onset)	6,042 / 19,492	*BSND - PCSK9*	T		1.00E-08	1.15	[91]
			CHD	86,995 / 56,682		T		9.00E-08	1.08	[89]
8	rs12239436	1p32.3	CHD	8,090 / 8,849	*MIR4422 - GOT2P1*	A		5.00E-06	0.09	[85]
9	rs2229238	1q21.3	CHD	13,949 / 11,032	*IL6R*	?	UTR-3	7.00E-07	1.45	[94]
10	rs1028771	1q25.3	CHD	8,090 / 8,849	*LAMC2*	A	intron	4.00E-06	0.22	[85]
11	rs12734338	1q32.1	CHD	94 from 32 families	*PPP1R12B*	G	intron	3.00E-07	29	[95]
12	rs7526425	1q32.3	CHD	8,090 / 8,849	*RD3 - SLC30A1*	?		1.00E-06	1.16	[85]
13	rs17465637	1q41	CHD	4,864 / 2,519	*MIA3*	C	intron	1.00E-06	1.20	[81]
			MI (early onset)	6,042 / 19,492		C		1.00E-09	1.14	[91]
			CHD	86,995 / 56,682		C		1.00E-08	1.14	[89]
14	rs744487	1q42.3	CHD	8,090 / 8,849	*TARBP1 - IRF2BP2*	A		5.00E-06	0.07	[85]
15	rs17672135	1q43	CHD	4,864 / 2,519	*FMN2*	T	intron	2.00E-06	1.43	[80]
16	rs2346177	2p21	CHD	8,090 / 8,849	*EPAS1 - TMEM247*	A		2.00E-06	0.07	[85]
17	rs11684202	2p23.3	CHD	8,090 / 8,849	*DTNB*	A	intron	6.00E-06	0.09	[85]

Table 1 (continued): Main GWAS findings for CAD / CHD / MI / MI early onset

	SNPs	Region	Disease/Trait	Sample Size	Mapped gene	Risk Allele	Context	p	OR or beta	Reference
18	rs13015955	2p24.1	CHD	8,090 / 8,849	*RNA5SP87 - KLHL29*	A		4.00E-07	0.18	[85]
19	rs2123536	2p24.1	CHD	6,534 / 26,932	*OSR1 - CISD1P1*	T		7.00E-11	1.12	[84]
20	rs4665630	2p24.1	CHD	8,090 / 8,849	*KLHL29*	?	intron	1.00E-07	1.21	[85]
21	rs7569328	2p24.1	CHD	8,090 / 8,849	*C2orf43 - APOB*	T		1.00E-07	0.10	[85]
22	rs13424957	2q24.3	CHD	8,090 / 8,849	*LOC101929633*	?	intron	3.00E-06	1.24	[85]
23	rs2080401	2q31.1	CHD	8,090 / 8,849	*HMGB1P4 - LINC01124*	A		7.00E-06	0.72	[85]
24	rs7586970	2q32.1	CHD	30,482 / 40,593	*TFPI*	?	missense (Asn ⇒ Ser)	9.00E-06	NR	[92]
25	rs840616	2q32.1	CHD	30,482 / 40,593	*IMPDH1P7 - CALCRL*	?		7.00E-07	NR	[92]
26	rs6725887	2q33.2	MI (early onset)	6,042 / 19,492	*WDR12*	C	intron	1.00E-08	1.17	[91]
			CHD	86,995 / 56,682		C		1.00E-09	1.14	[89]
			CAD	109,124		C		2.00E-08	1.14	[90]
27	rs17458018	2q35	CHD	13,949 / 11,032	*FN1*	?	intron	7.00E-06	1.22	[94]
28	rs2943634	2q36.3	CHD	4,864 / 2,519	*NYAP2 - MIR5702*	C		2.00E-07	1.21	[81]
29	rs10933436	2q37.1	CHD	86,995 / 56,682	*INPP5D*	A	intron	7.00E-06	1.06	[89]
30	rs4618210	3p24.3	MI	4,864 / 39,809	*PLCL2*	G	intron	3.00E-09	1.10	[96]
31	rs7651039	3p25.1	CHD	86,995 / 56,682	*BTD*	C	intron	2.00E-06	1.06	[89]
32	rs2306374	3q22.3	CHD	86,995 / 56,682	*MRAS*	C	intron	3.00E-08	1.12	[89]
33	rs9818870	3q22.3	CHD	2,520 / 38,253	*MRAS*	T	UTR-3	7.00E-13	1.15	[97]
			CAD	109,124		T		1.00E-07	1.11	[90]
34	rs11920719	3q26.2	CHD	8,090 / 8,849	*TNIK*	A	intron	4.00E-06	0.10	[85]
35	rs17589290	4q25	CHD	8,090 / 8,849	*RPL36AP23 - CCDC34P1*	?		6.00E-06	1.43	[85]
36	rs3853444	4q25	CHD	94 from 32 families	*PITX2 - MIR297*	G		5.00E-06	7.69	[95]
37	rs10026364	4q28.3	CHD	8,090 / 8,849	*PES1P1 - RPS2P27*	T		4.00E-06	1.28	[85]
38	rs1395821	4q31.22	CHD	30,482 / 40,593	*TTC29 - MIR548G*	?		7.00E-07	NR	[92]

Table 1 (continued): Main GWAS findings for CAD / CHD / MI / MI early onset

	SNPs	Region	Disease/Trait	Sample Size	Mapped gene	Risk Allele	Context	p	OR or beta	Reference
39	rs1878406	4q31.22	CAD	109,124	*PRMT5P1 - EDNRA*	T		1.00E-06	1.1	[90]
40	rs1842896	4q32.1	CHD	6,534 / 26,932	*MTND1P22 - GUCY1A3*	T		1.00E-11	1.14	[84]
41	rs11748327	5p15.33	MI	1,733 / 11,397	*IRX1 - LINC01020*	?		5.00E-13	1.25	[98]
42	rs17577085	5q31.3	CHD	8,090 / 8,849	*SPRY4 - RPS12P10*	?		4.00E-06	2.63	[85]
43	rs13161895	5q35.3	CHD	8,090 / 8,849	*RNF130*	T	intron	6.00E-07	0.15	[85]
44	rs6905288	6p21.1	CHD	13,949 / 11,032	*TRNAI25*	T		7.00E-08	1.23	[94]
45	rs12205331	6p21.31	CAD	109,124	*ANKS1A*	T	intron	6.00E-06	1.08	[90]
46	rs17609940	6p21.31	CHD	86,995 / 56,682	*ANKS1A*	G	intron	1.00E-08	1.07	[89]
47	rs11752643	6p21.32	CHD	2,143 / 9,928	*TRNAI25*	T		5.00E-07	1.26	[83]
48	rs9268402	6p21.32	CHD	6,534 / 26,932	*C6orf10*	G	nearGene-5	3.00E-15	1.16	[84]
49	rs3869109	6p21.33	CHD	13,949 / 11,032	*TRNAI25*	G		1.00E-09	1.14	[94]
50	rs12526453	6p24.1	MI (early onset)	6,042 / 19,492	*PHACTR1*	C	intron	1.00E-09	1.12	[91]
			CHD	86,995 / 56,682		C		1.00E-09	1.10	[89]
51	rs1332844	6p24.1	CHD	30,482 / 40,593	*PHACTR1*	T	intron	6.00E-08	1.11	[92]
52	rs9349379	6p24.1	CHD	30,482 / 40,593	*PHACTR1*	?	intron	9.00E-26	NR	[92]
			CHD	30,482 / 40,593		?		9.00E-26	NR	[93]
			CHD	1,949 / 2,547		G		8.00E-10	1.34	[99]
			CHD	6,534 / 26,932		G		2.00E-09	1.15	[84]
53	rs9369640	6p24.1	CAD	109,124	*PHACTR1*	C	intron	3.00E-11	1.10	[90]
54	rs16893526	6q14.1	CHD	5,031 / 54,758	*FAM46A - IBTK*	G		5.00E-06	1.13	[100]
55	rs12200560	6q16.1	CHD	13,949 / 11,032	*FHL5 - RPS7P8*	?		6.00E-07	1.11	[94]
56	rs12190287	6q23.2	CHD	86,995 / 56,682	*TCF21*	C	UTR-3	1.00E-12	1.08	[89]
			CAD	109,124		G		2.00E-09	1.11	[90]
57	rs12524865	6q23.2	CHD	6,534 / 26,932	*LOC100507308*	C	intron	2.00E-07	1.11	[84]

Table 1 (continued): Main GWAS findings for CAD / CHD / MI / MI early onset

	SNPs	Region	Disease/Trait	Sample Size	Mapped gene	Risk Allele	Context	p	OR or beta	Reference
58	rs6922269	6q25.1	CHD	4,864 / 2,519	*MTHFD1L*	A	intron	3.00E-08	1.23	[81]
59	rs675026	6q25.2	CHD	8,090 / 8,849	*OPRM1*	?	cds-synon	5.00E-06	1.20	[85]
60	rs2048327	6q25.3	CAD	109,124	*SLC22A3*	C	intron	1.00E-06	1.07	[90]
61	rs365302	6q25.3	CHD	5,031 / 54,758	*FNDC1*	C	intron	8.00E-07	1.11	[100]
62	rs3798220	6q25.3	CHD	86,995 / 56,682	*LPA*	C	missense (Ile ⇒ Met)	3.00E-11	1.51	[89]
63	rs7801190	7q22.1	CHD	8,090 / 8,849	*SLC12A9*	C	intron	3.00E-08	1.31	[85]
64	rs10953541	7q22.3	CHD	30,482 / 40,593	*BCAP29*	C	intron	3.00E-08	1.08	[92]
65	rs7808424	7q31.2	CHD	86,995 / 56,682	*ASZ1*	G	nearGene-5	1.00E-06	1.10	[89]
66	rs11556924	7q32.2	CHD	86,995 / 56,682	*ZC3HC1*	C	missense (Arg ⇒ His)	9.00E-18	1.09	[89]
			CAD	109,124		T		3.00E-10	1.10	[90]
67	rs13232179	7q36.1	CHD	8,090 / 8,849	*WDR86-AS1 - CRYGN*	A		1.00E-06	1.67	[85]
68	rs264	8p21.3	CAD	109,124	*LPL*	A	intron	3.00E-07	1.11	[90]
69	rs6601299	8p23.1	CHD	8,090 / 8,849	*LOC157273*	T	intron	1.00E-08	0.14	[85]
70	rs4875320	8p23.2	CHD	8,090 / 8,849	*CSMD1*	A	intron	6.00E-06	0.10	[85]
71	rs10757274	9p21.3	CHD	6,534 / 26,932	*CDKN2B-AS1*	G	intron	8.00E-45	1.37	[84]
72	rs10757278	9p21.3	MI	8,335 / 9,289	*UBA52P6 - DMRTA1*	G		1.00E-20	1.28	[79]
73	rs1333049	9p21.3	CHD	4,864 / 2,519	*UBA52P6 - DMRTA1*	C		1.00E-13	1.47	[80]
			CHD	4,864 / 2,519		C		3.00E-19	1.36	[81]
			CHD	5,031 / 54,758		C		7.00E-58	1.27	[100]
			CAD	109,124		C		3.00E-56	1.24	[90]
74	rs4977574	9p21.3	MI (early onset)	6,042 / 19,492	*CDKN2B-AS1*	G	intron	3.00E-44	1.29	[91]
			CHD	86,995 / 56,682		G		1.00E-22	1.29	[89]
			CHD	30,482 / 40,593		G		2.00E-25	1.20	[92]
			MI	4,864 / 39,809		C		8.00E-06	1.22	[96]

Table 1 (continued): Main GWAS findings for CAD / CHD / MI / MI early onset

	SNPs	Region	Disease/Trait	Sample Size	Mapped gene	Risk Allele	Context	p	OR or beta	Reference
75	rs1333042	9p21.3	CHD	5,714 / 8,028	*CDKN2B-AS1*	?	intron	1.00E-09	1.30	[82]
76	rs7865618	9p21.3	CHD	5,031 / 54,758	*CDKN2B-AS1*	A	intron	2.00E-27	1.18	[100]
77	rs944797	9p21.3	CHD	2,143 / 9,928	*CDKN2B-AS1*	C	intron	6.00E-16	1.25	[83]
78	rs4743150	9q22.33	CHD	30,482 / 40,593	*HEMGN - ANP32B*	?		5.00E-06	NR	[92]
79	rs2515629	9q31.1	CHD	8,090 / 8,849	*ABCA1*	A	intron	5.00E-07	0.12	[85]
80	rs514659	9q34.2	CHD	10,034 / 19,169	*ABO*	C	intron	8.00E-09	1.21	[101]
81	rs579459	9q34.2	CHD	86,995 / 56,682	*ABO - SURF6*	C		4.00E-14	1.10	[89]
			CAD	109,124		C		2.00E-07	1.10	[90]
82	rs2505083	10p11.23	CHD	30,482 / 40,593	*KIAA1462*	C	intron	4.00E-08	1.07	[92]
83	rs3739998	10p11.23	CHD	2,905 / 16,131	*KIAA1462*	C	missense (Ser ⇒ Thr)	1.00E-11	1.15	[102]
84	rs1746048	10q11.21	MI (early onset)	6,042 / 19,492	*LINC00841 - CXCL12*	C		7.00E-09	1.17	[91]
			CHD	86,995 / 56,682		C		3.00E-10	1.09	[89]
85	rs501120	10q11.21	CHD	4,864 / 2,519	*LINC00841 - CXCL12*	T		9.00E-08	1.33	[81]
			CAD	109,124		C		2.00E-06	1.09	[90]
86	rs1412444	10q23.31	CHD	30,482 / 40,593	*LIPA*	T	intron	3.00E-13	1.09	[92]
			CHD	5,031 / 54,758		T		4.00E-08	1.10	[100]
87	rs12413409	10q24.32	CHD	86,995 / 56,682	*CNNM2*	G	intron	1.00E-09	1.12	[89]
			CHD	30,482 / 40,593		?		4.00E-06	NR	[92]
			CAD	109,124		A		1.00E-06	1.12	[90]
88	rs7901695	10q25.2	CHD	8,090 / 8,849	*TCF7L2*	?	intron	1.00E-06	1.19	[85]
89	rs10895547	11q22.3	CHD	8,090 / 8,849	*PDGFD*	T	intron	3.00E-06	0.07	[85]
90	rs974819	11q22.3	CHD	30,482 / 40,593	*MTND1P36 - MIR4693*	T		2.00E-09	1.07	[92]
91	rs12269901	11q23.3	CHD	8,090 / 8,849	*RPS27P19 - PAFAH1B2*	C		2.00E-06	0.07	[85]
92	rs1263173	11q23.3	CHD	8,090 / 8,849	*APOA5 - APOA4*	A		2.00E-07	0.09	[85]

Table 1 (continued): Main GWAS findings for CAD / CHD / MI / MI early onset

	SNPs	Region	Disease/Trait	Sample Size	Mapped gene	Risk Allele	Context	p	OR or beta	Reference
93	rs9326246	11q23.3	CAD	109,124	*RPL15P15 - BUD13*	C		3.00E-07	1.15	[90]
94	rs964184	11q23.3	CHD	86,995 / 56,682	*ZPR1*	G	intron	1.00E-17	1.13	[89]
95	rs4937126	11q24.2	CHD	86,995 / 56,682	*ST3GAL4*	G	intron	5.00E-06	1.06	[89]
96	rs7136259	12q21.33	CHD	6,534 / 26,932	*ATP2B1*	T	intron	6.00E-10	1.11	[84]
97	rs3782889	12q24.11	CHD	5,714 / 8,028	*MYL2*	C	intron	4.00E-14	1.26	[82]
98	rs886126	12q24.11	CHD	5,714 / 8,028	*CUX2*	T	intron	1.00E-06	1.14	[82]
99	rs11066015	12q24.12	CHD	5,714 / 8,028	*ACAD10*	A	intron	5.00E-11	1.41	[82]
100	rs3184504	12q24.12	CHD	86,995 / 56,682	*SH2B3*	T	missense (Trp ⇒ Arg)	6.00E-06	1.07	[89]
			CAD	109,124		T		9.00E-07	1.07	[90]
101	rs3782886	12q24.12	MI	4,864 / 39,809	-	A		1.00E-14	1.46	[96]
102	rs671	12q24.12	CHD	2,143 / 9,928	*ALDH2*	A	missense (Glu ⇒ Lys)	2.00E-34	1.43	[83]
103	rs11066280	12q24.13	CHD	6,534 / 26,932	*HECTD4*	A	intron	2.00E-11	1.19	[84]
104	rs2259816	12q24.31	CHD	2,520 / 38,253	*HNF1A*	T	intron	5.00E-07	1.08	[97]
105	rs9508025	13q12.3	CHD	5,714 / 8,028	*FLT1*	C	intron	6.00E-07	1.14	[82]
106	rs9546711	13q31.1	CHD	8,090 / 8,849	*LINC00333*	A		2.00E-06	1.66	[85]
107	rs7323893	13q31.2	CHD	8,090 / 8,849	*TET1P1 - RPL29P29*	T		1.00E-07	0.14	[85]
108	rs4773144	13q34	CHD	86,995 / 56,682	*COL4A1;COL4A2*	G	nearGene-5; intron	4.00E-09	1.07	[89]
			CAD	109,124		G		2.00E-06	1.08	[90]
109	rs2895811	14q32.2	CHD	86,995 / 56,682	*HHIPL1*	C	intron	1.00E-10	1.07	[89]
110	rs937254	15q21.3	CHD	8,090 / 8,849	*GCOM1;MYZAP*	A	intron; intron	1.00E-06	0.08	[85]
111	rs12595292	15q22.31	CHD	8,090 / 8,849	*PLEKHO2*	A	cds-synon	9.00E-06	0.11	[85]
112	rs17228212	15q22.33	CHD	4,864 / 2,519	*SMAD3*	C	intron	2.00E-07	1.21	[81]
113	rs1445021	15q23	CHD	8,090 / 8,849	*ITGA11 - CORO2B*	A		9.00E-06	0.14	[85]
114	rs2472299	15q24.1	CHD	30,482 / 40,593	*CYP1A1 - CYP1A2*	?		3.00E-06	NR	[92]

Table 1 (continued): Main GWAS findings for CAD / CHD / MI / MI early onset

	SNPs	Region	Disease/Trait	Sample Size	Mapped gene	Risk Allele	Context	p	OR or beta	Reference
115	rs1994016	15q25.1	CHD	10,034 / 19,169	*ADAMTS7*	C	intron	5.00E-13	1.19	[101]
116	rs3825807	15q25.1	CHD	86,995 / 56,682	*ADAMTS7*	A	missense (Ser ⇒ Pro)	1.00E-12	1.08	[89]
117	rs4380028	15q25.1	CHD	30,482 / 40,593	*ADAMTS7 - TRNAK6*	C		4.00E-09	1.07	[92]
118	rs7173743	15q25.1	CAD	109,124	*ADAMTS7 - TRNAK6*	C		7.00E-08	1.08	[90]
119	rs3883013	15q25.2	CHD	94 from 32 families	*UBE2Q2P1*	G	intron	3.00E-07	29	[95]
120	rs7203193	16p13.13	CHD	8,090 / 8,849	*LITAF*	A	nearGene-3	3.00E-06	0.08	[85]
121	rs16965039	16q13	CHD	8,090 / 8,849	*NLRC5*	T	intron	6.00E-07	0.14	[85]
122	rs3729639	16q22.1	CHD	8,090 / 8,849	*E2F4;EXOC3L1*	T	nearGene-5;	2.00E-11	0.09	[85]
123	rs8060686	16q22.1	CHD	8,090 / 8,849	*EDC4*	T	cds-synon	8.00E-06	0.07	[85]
124	rs16971384	16q22.3	CHD	8,090 / 8,849	*ZFHX3*	A	intron	5.00E-06	0.07	[85]
125	rs8055236	16q23.3	CHD	4,864 / 2,519	*CDH13*	G	intron	6.00E-06	1.91	[80]
126	rs12936587	17p11.2	CHD	86,995 / 56,682	*EEF1A1P43 - RAI1*	G		4.00E-10	1.07	[89]
			CAD	109,124		A		2.00E-07	1.08	[90]
127	rs1231206	17p13.3	CHD	86,995 / 56,682	*SMG6*	A	intron	9.00E-10	1.07	[89]
128	rs216172	17p13.3	CHD	86,995 / 56,682	*SMG6*	C	intron	1.00E-09	1.07	[89]
129	rs2281727	17p13.3	CAD	109,124	*SMG6*	G	intron	1.00E-07	1.07	[90]
130	rs11650066	17q12	CHD	30,482 / 40,593	*ASIC2*	?	intron	6.00E-06	NR	[92]
131	rs46522	17q21.32	CHD	86,995 / 56,682	*UBE2Z*	T	intron	2.00E-08	1.06	[89]
132	rs6504218	17q23.3	CHD	30,482 / 40,593	*PECAM1*	?	intron	1.00E-06	NR	[92]
133	rs1122608	19p13.2	MI (early onset)	6,042 / 19,492	*SMARCA4*	G	intron	2.00E-09	1.15	[91]
			CHD	86,995 / 56,682		G		1.00E-09	1.14	[89]
			CAD	109,124		T		3.00E-11	1.14	[90]
134	rs11669133	19p13.2	CHD	8,090 / 8,849	*SMARCA4*	A	intron	1.00E-08	0.17	[85]
135	rs11671653	19p13.2	CHD	8,090 / 8,849	*DNM2*	A	intron	9.00E-07	0.11	[85]

Table 1 (continued): Main GWAS findings for CAD / CHD / MI / MI early onset

	SNPs	Region	Disease/Trait	Sample Size	Mapped gene	Risk Allele	Context	p	OR or beta	Reference
136	rs4804155	19p13.2	CHD	8,090 / 8,849	*DOCK6*	C	intron	5.00E-06	0.08	[85]
137	rs3803915	19p13.3	MI	4,864 / 39,809	*AP3D1 - DOT1L*	C		4.00E-09	1.12	[96]
138	rs1475591	21q22.11	CHD	8,090 / 8,849	*UBE3AP2 - TIAM1*	T		6.00E-06	1.18	[85]
139	rs9982601	21q22.11	MI (early onset)	6,042 / 19,492	*LINC00310 - KCNE2*	T		6.00E-11	1.20	[91]
			CHD	86,995 / 56,682		T		4.00E-10	1.18	[89]
			CAD	109,124		T		3.00E-10	1.18	[90]
140	rs1735151	21q22.2	CHD	8,090 / 8,849	*IGSF5*	T	intron	9.00E-06	1.16	[85]
141	rs688034	22q12.1	CHD	4,864 / 2,519	*SEZ6L*	T	intron	4.00E-06	1.11	[80]
142	rs5943057	Xq23	CHD	30,482 / 40,593	*CHRDL1*	?	intron	9.00E-07	NR	[92]
143	rs1190739	Xq26.3	CHD	8,090 / 8,849	*SNORD61 - SRRM1P3*	T		5.00E-06	0.07	[85]
144	rs5904726	Xq27.3	CHD	8,090 / 8,849	*MIR508 - MIR514B*	A		9.00E-06	0.06	[85]

CAD: coronary artery disease; CHD: coronary heart disease; MI: myocardial infarction; OR: odds ratio; UTR: untranslated region

Sample size was displayed as Initial Sample Size / Replication Sample Size

that the enhancer interval in 9p21.3 can physically interact with methylthioadenosine phosphorylase (MTAP), *CDKN2A/B* and downstream of INFA21 in human vascular endothelium cells (HUVEC) [103]. The structure of the chromatin and the transcriptional regulation of the 9p21 region could be strongly influenced by activation of interferon gamma (*IFNγ*) thus a link between 9p21.3 and response to inflammatory signaling in vascular cells was established [103].

As mentioned above, 95 of the CAD associated SNPs are within or near protein-coding genes. Some of these genes are related to CAD risk factors, such as cholesteryl ester transfer protein (*CETP*) [104], a gene involved in the transportation of cholesteryl ester from HDL to other lipoproteins and apolipoprotein A5 (*APOA5*), a gene regulating the plasma level of a major CAD risk factor, triglyceride [105]. However, many genetic variants revealed by GWAS lack of biological relevance and the mechanisms involved are largely unknown, such as dynamin 2 (*DNM2*), the protein encoded by which is one of the subfamilies of GTP-binding proteins. This is one of the drawbacks of GWAS. It can easily discovered SNPs associated with a disease but on its own, is unable to specify the casual relationship involved [106].

Ethnicity also plays an essential role in identification of CAD related genetic variations. Some SNPs are generally transferable between ethnic groups, such as the genetic variants from the 9p21.3 region and SNPs from 6p24.1 region [84, 99] while some other SNPs have been identified specifically in certain ethnicities thus far.

One of the examples is rs6903956 in the *C6orf105* region. The association was first identified in a GWAS conducted in Han Chinese population with a discovery cohort of 230 cases and 230 controls followed by a validation cohort of 572 cases and 436 cohorts. The association was then replicated in a larger cohort of 2,668 cases and 3,917 controls. The minor allele A of rs6903956 was found to reduce mRNA expression of *C6orf105* and increase risk of CAD [46]. The SNP was also reported to be associated with angiographical characteristics of coronary atherosclerosis in a Chinese population [107]. *C6orf105* was later found to code for a transmembrane protein which could regulate *TFPI* both in native condition and treated with androgen in the aspect of mRNA expression, cellular distribution and cell associated anticoagulant activity [108]. Although the association failed to be replicated in a meta-analysis study conducted in two Chinese cohorts with larger sample size of 1,515 cases and 5,019 controls in total, it has been replicated in other independent Chinese cohorts [107], including the Singaporean Chinese [47]. The mechanism underlying this association is still unknown.

2.2.2 GWAS of CAD related risk factor traits

CAD related risk factor traits including HDL cholesterol, LDL cholesterol, TG, diabetes, fasting glucose related traits, blood pressure (BP, systolic/diastolic blood pressure), obesity, BMI and C-reactive protein (CRP). To date, 853 SNPs from 325 loci were reported to be associated with these CAD related risk factor traits. Among these SNPs, 518 SNPs (60.73%) are within or near protein-coding genes and 75 of

them are known to be functional.

There are 110 SNPs from 71 loci that were found to be associated with BP, including SBP and DBP. The first GWAS on BP was conducted in Framingham Heart Study in 2007 and weak association was found between SNPs in the renin-angiotensin-aldosterone pathway and BP [109]. A total of 211 SNPs from 107 loci had an association with BMI or obesity. The first BMI GWAS was conducted in 2007 and identified a genetic variant from *FTO* gene, which has shown the strongest association with BMI and obesity [110, 111] thus far. In total, 48 SNPs from 23 risk loci had an effect on CRP level. The first GWAS of CRP was conducted in a European population with a discovery cohort of 909 individuals followed by a replication with 5,106 subjects. The study found that genetic variants from hepatocyte nuclear factor-1α (*HNF1A*) gene could affect CRP level [112]. A total of 209 SNPs from 123 loci were reported to be associated with type 2 diabetes, including fasting glucose-related traits. The first GWAS for diabetes was carried out in Caucasians in 2007 with a discovery population of 661 cases and 614 controls followed by a replication cohort with 2,617 cases and 2,894 controls. The study identified four loci associated with risk for diabetes, including one known association with transcription factor 7 like 2 (*TCF7L2*) gene and three novel associations [113]. In total, 292 SNPs from 134 risk loci were reported to be associated with plasma lipid levels, including HDL, LDL and TG. The first HDL GWAS was carried out in a cohort with a discovery population of 8,656 European ancestry individuals followed

by a replication population of 11,437 European ancestry individuals. The study identified ten SNPs that were associated with plasma HDL levels [114], some of them was proven to implicate in lipid metabolism while some were newly identified. The first LDL GWAS was conducted in 2008 and confirmed the association between SNPs close to proline and serine rich coiled-coil 1 (*PSRC1*) gene and LDL level in 1,955 European ancestry hypertensive individuals and replicated the association in 2,033 European ancestry individuals from 519 families as well as 1,461 European ancestry twins [115]. In 2007, the first TG GWAS was carried out in 5,217 Caucasians. The study identified and confirmed a novel association between genetic variant from glucokinase regulatory protein (*GCKR*) gene and serum TG level [116].

2.2.3 Genotype calling

As mentioned previously, GWAS is usually an investigation of many SNPs in a group of cases and controls to determine if any SNP is associated with a diseases trait. It is based on genotyping of a subset of SNPs that can provide as much as the coverage of the entire genome by linkage disequilibrium (LD) using genotype arrays. Bi-allelic SNPs will have three genotypes, major allele homozygote (AA), heterozygote (Aa) and minor allele homozygote (aa). The process of genotype determination for an individual at a specific SNP site by estimating the probability using genotype calling algorithms for the three genotypes is termed genotype calling. Cutoff will be applied to determine the genotypes. Only those with values above the cutoff will be accepted while the rest will be set as missing. Early studies used Phredtype quality

score of Q20 (Q_{Phred} = 20) as fixed cutoff and determined genotypes by counting the number of times each allele is observed. Recent studies incorporate uncertainty in a probabilistic framework to deal with the issues caused by fixed cutoff, such as under-calling of heterozygous genotypes [117]. Development of genotype calling algorithms and choosing of cutoff are crucial for data quality. It should be also noted that the minor allele frequency (MAF) can also affect genotype calling. The accuracy is mostly gained for SNPs moderate or high allele frequencies [117].

2.2.4 Quality control

Quality control (QC) is an essential process in GWAS to minimize bias and false-positive or false-negative findings. It comprises SNP QC and sample QC.

2.2.4.1 SNP QC

SNP QC, also called per-marker QC, removes SNPs that had at least one of the following features (1) SNPs with excessive missing genotype (> 5.0%), (2) SNPs with significant departure from Hardy-Weinberg Equilibrium (HWE, $P < 10^{-6}$-10^{-4}) in controls, (3) SNPs with significantly different missingness in cases and controls, and (4) monomorphic SNPs or SNPs with very low minor allele frequency (MAF, < 1.0%) [118].

Excessive missing of genotypes or significantly different missingness in cases and controls indicate the poor quality of the genotype calling for the specific SNP. HWE

is a statement that in the absence of evolutionary influences, such as mate choice and mutation, the allele and genotype frequencies in a population will stay constant from generation to generation. It is normally examined by Pearson's χ^2 test. Significant departure from HWE indicates genotype calling errors and selection bias [119]. With the use of current genotype calling algorithms, it is difficult to determine the genotypes of rare variants. Even though the genotype calling is correct, association signals observed at the site of these rare variants are less robust as they are driven by the genotypes of only a few individuals. Thus those SNPs with MAF less than 0.01 should be removed from further analysis.

2.2.4.2 Sample QC

Sample QC, also called per-individual QC, removes individuals that had at least one of the following features: (1) individuals with discordant information on gender, (2) individuals with excessive heterozygosity or missingness of genotypes, (3) duplicates (monozygotic twins) or related individuals (first-degree relatives), (4) individuals with divergent ancestry or discordant ethnic information [118].

Excessive missingness of genotypes indicates the poor quality of DNA samples. Heterozygosity is calculated as $(N - O)/N$, where N is the total number of non-missing genotypes and O is the observed number of homozygous genotypes for an individual. Excessive of heterozygosity indicates contamination or inbreeding of DNA samples. The presence of duplicates (monozygotic twins) or related

individuals (first-degree relatives) will introduce bias into studies since genotype within families will be over represented. The familial relationship can be checked by identity by descent (IBD). It calculates the shared allele proportion for each pair of samples for independent SNPs. IBD of one means the samples are duplicates or monozygotic twins and IBD of 0.5 shows first degree familial relationship. If individuals with divergent ancestry or discordant ethnic information are included in the study, the associations identified might be due to different population origins and thus spurious.

2.2.5 Linkage disequilibrium

LD is the non-random and dependent association between alleles at different loci. If the frequency of association of different alleles at different loci were different from what is expected when the loci were independent and associated randomly, they were in LD with each other [120]. Many factors can affect LD between different loci, such as recombination rate, selection, population structure and mutation rate. The LD between SNPs was calculated by the pairwise correlations (Pearson correlation) [121] using STATA 12.0 (Stata Corp, College station, TX).

2.2.6 Imputation

Genotype imputation is performed as a key step in most GWAS that can predict genotypes for SNPs not present on the genotyping chip [122]. This is achieved by using known haplotypes in a population based on high LD. It could largely increase

the number of SNPs assessed for association and enables meta-analysis of GWAS across diverse cohorts or genotyped using different array chips. Imputation is carried out by combining GWAS data based on tagging SNPs and a reference panel that have been genotyped for a larger number of genetic variants, such as those from the Hapmap [123] and 1000 Genome Project [124]. The most frequently used software for imputation currently as well as in our study is IMPUTE [125].

2.2.7 Meta-analysis

Meta-analysis uses approaches from statistics to combines the data and results from multiple studies. It is under the theory that a common truth behind all conceptually similar scientific studies might have certain measurement errors within individual studies but it can be revealed in a pooled estimate closest to the unknown common truth. Meta-analysis can increase statistical power in the pooled study, improve estimates of effect size and resolve uncertainty between individual studies. Meta-analysis makes use of a common statistical measure among individual studies termed effect size with a standard error (SE). A weighted average is calculated for effect size, which usually considers the sample sizes and study quality of different studies. Several methods could be used to do the meta-analysis, such as the P value meta-analysis, fixed effects meta-analysis, random effect meta-analysis, Bayesian approach meta-analysis, multivariate approaches meta-analysis [126]. In this thesis, inverse variance-weighted, fixed-effects meta-analysis was used to meta-analyze the results from individual cohorts since fixed effects meta-analysis is the most popular

and powerful approach for prioritizing and discovering phenotype-associated SNPs [127]. It maximizes discovery power compared to random effects models [128]. However, bias might exist if there is excessive heterogeneity [126]. Since the cohorts involved in the current studies are all Singaporean Chinese, we assumed that effect of each risk allele is the same in individual cohorts and Cochran's Q test was used to measure between-study heterogeneity.

2.2.8 Multiple testing

As mentioned above, GWAS have several issues and limitations. The issue of multiple testing is one of the limitations and it has been known that "the GWA approach can be problematic because the massive number of statistical tests performed presents an unprecedented potential for false-positive results" [129].

Multiple testing usually occurs when a study takes several statistical inferences into consideration simultaneously [130]. When a great number of statistical tests are performed, it will be more likely to introduce errors in inference or incorrectly reject the null hypothesis. Several statistical methods have been developed to avoid multiple testing problems, such as false discovery rate (FDR) and Bonferroni correction. FDR conceptualizes rate of type I error in null hypothesis testing when multiple testing are conducted. It controls the expected proportion of rejecting null hypotheses incorrectly [131]. FDR is calculated as $V / (V+S)$, where V is the total number of false positives (type I error) and S is the total number of true positives.

FDR is less stringent compared to Bonferroni correction. Bonferroni correction also controls for type I error. It maintains the familywise error rate (FWER) by using a more stringent statistical significance level, calculated as α / N, where α is the significance level and N is the total number of independent statistical tests.

2.3 Framingham Heart Study and development of risk prediction models

2.3.1 Framingham Heart Study

In 1948, it was noted that 44% of total deaths were attributed to CVD, which was 20% higher than the proportion in 1940 [132]. However, almost nothing was known for the epidemiology of arteriosclerotic or hypertensive CVD at that time and it was believed that clogging and narrowing of arteries were normal phenomena due to aging. The urgent need to elucidate the causes of CVD led to the inauguration of the FHS. This is a long-term, longitudinal study conducted on the residents of the town Framingham, Massachusetts, USA. It is the most seminal and well-designed prospective study in CVD epidemiology. The investigation was inaugurated in 1948 and recruited 5,209 healthy individuals aged 30 to 62 as its study subjects. It is still on-going currently and has two collateral investigations, the Offspring study initiated in 1971 and the Third generation study started in 2002 [133]. Some studies for CHD used FHS as a model for study design [134, 135]. Much of the current understanding of CVD, such as the contribution of lifestyle environmental factors and genetic factors to cardiac health, is obtained from the FHS. In addition, the term

'risk factor' was first introduced by this study. The FHS identifies a great many of risk factors related to CVD. In 1956, it was revealed that risk of CVD was significantly associated with age and gender, with male having higher risk than female [136]. In 1960, FHS found cigarette smoking was a significant risk factor in the development of heart disease and that the association was dose related. The finding was confirmed later along with other studies and further revealed that cigarette smoking can lead to angina pectoris, MI and even coronary death [137, 138]. Later in 1961, high blood pressure, elevated serum cholesterol and electrocardiogram abnormalities were found to increase the risk of heart disease in FHS [139]. In 1967, it was identified that obesity [140] can increases risk while physical activities can decrease risk [141]. In 1970, an association was found between high blood pressure and increased risk of stroke [142] and atrial fibrillation can increase stroke risk by 5-fold [143]. In 1976, it was shown that postmenopausal women have higher chance of getting heart disease than women who are premenopausal [144]. In 1978, psychosocial factors were found to have an effect on heart disease risk [145]. In 1988, it was found that in contrast to LDL and total cholesterol level, high levels of HDL cholesterol could reduce risk of death [146]. In 1994, an association was found between enlarged left ventricle and increased stroke risk [147]. In 1998, an association was identified between atrial fibrillation and risk of all-cause mortality [148]. In 2001, it was found that in addition to hypertension (SBP no less than 140 mm Hg and/or diastolic blood pressure (DBP) no less than 90 mm Hg), high normal blood pressure, also called pre-hypertension (SBP of 120-139 mm Hg and/or

DBP of 80-89 mm Hg) could also increase risk of CVD [149]. In 2002, obesity was confirmed to be a risk factor for heart failure [150]. In 2010, sleep apnea was found to be associated with increased risk of stroke [151].

2.3.2 Risk prediction models

CHD is a chronic disease and the atherosclerotic process begins long before disease onset. Many contributing risk factors modulate the probability of developing CHD. Being able to identify individuals who are apparently healthy but are at high risk of developing CHD would be important for implementing early intervention and treatment.

As mentioned, many CHD risk factors have been identified in FHS, which makes it possible to use phenotypic risk factors to predict the probability of healthy individuals getting CHD after a couple of years. In 1991, Anderson et al [152] developed the first prediction equation based on the Framingham data using a non-proportional hazards Weibull accelerated failure time regression model. Prior to this study, most prediction equations used fixed follow-up period [153, 154]. The inclusion of the time period improved the accuracy of the prediction model. However, in this study, the authors only derived the prediction equation using CHD, which includes MI, angina pectoris, coronary insufficiency, and sudden death, as the outcome. For the risk predictors, they only made use of age, SBP, cholesterol, metropolitan relative weight and cigarette smoking. The definition for the outcome was ambiguous and

only a few risk factors were taken into consideration. Aware of the limitations of the study, Anderson et al revised the model in the same year [155]. In this updated study, more phenotypic risk factors were taken into account, including age, sex, SBP / DBP, cholesterol, HDL, smoking, diabetes and electrocardiography (ECG-LVH). Moreover, a point score algorithm was developed in the same study, which enabled the estimation of CHD risk for middle-aged patients by assigning a point score to each risk factor and then added up together. The point score algorithm would be more applicable in clinical use than the equations. The issue is that the updated study still mixed several CVD endpoints together, such as stroke, transient ischemia and CHD. Although they are all under the category of CVD, they still have differences in origins. To address this issue, the same group of authors developed separate prediction equations for several CVD endpoints, including MI, CHD, death from CHD, stroke, CVD, and death from CVD [156]. It was found that most estimation of predicted probabilities was quite accurate and a separate equation was desirable for stroke. In 1998, Wilson et al [157] developed a simplified coronary prediction model, building on age, blood pressure, cigarette smoking, diabetes, HDL and cholesterol / LDL-C for males and females separately. Blood pressure was categorized into the following: optimal (SBP less than 120 mm Hg and DBP less than 80 mm Hg), normal BP (SBP: 120-129 mm Hg or DBP: 80-84 mm Hg), high normal BP (SBP: 130-139 mm Hg or DBP: 85-89 mm Hg), hypertension stage I (SBP: 140-159 mm Hg or DBP 90-99 mm Hg) and hypertension stage II-IV (SBP no less than 160 or DBP no less than 100 mm Hg) according to Fifth Joint National

Committee on Hypertension (JNC-V) definitions [158]. Total cholesterol (less than 200, 200-239, 240-279 and no less than 280 mg/dL), LDL (less than 130, 130-159 and no less than 160 mg/dL) and HDL (less than 35, 35-59 and no less than 60 mg/dL) were all grouped into categorical variables according to National Cholesterol Education Program, Adult Treatment Panel II (NCEP ATP II) guidelines [159]. The model developed in this study was much simpler than previous ones and included risk factors commonly known in recent years. In addition, the score sheet developed in this study was much more systematic and applicable. As a result, the model has been widely used since then. It allowed physicians to predict multivariate CHD risk in patients without overt symptom. After the risk prediction equations were developed and validated in the FHS, researchers began to be interested in the performance of the models in various non-US cohorts [160-163]. Some studies found the performance of the FHS equations were acceptably accurate [160] while other studies found that the FHS equations would over-estimate individual risk in their cohorts [161-163]. Since the performance of the FHS equation was not satisfying in most of the non-US cohorts, recalibration of the model is necessary to improve the prediction accuracy. In 2001, D'Agostino Sr et al first validated the FHS equation in 6 prospectively studied and ethnically diverse cohorts [164]. It was found that the FHS equation performed reasonably well for white men and women and for black men and women for prediction of CHD events within 5 years of follow-up while the equation over-estimated the risk of 5-year CHD events for Japanese American, Hispanic men and Native American women. In the recalibrated

models, the regression coefficients were from the FHS while the mean values of the risk factors and average incidence rate were replaced by those estimated from the local cohorts. After recalibration by taking into consideration the different prevalence of risk factors and underlying rates of developing CHD, the recalibrated FHS equation performed well in all the cohorts. In 2004, the same recalibration method was applied to a large Chinese population [165]. It was also found that after recalibration, the model no longer over-estimated CHD risk in Chinese, which indicated the effectiveness of the recalibration method.

Since CHD is a complex disease that both genetic, lifestyle factors and their interactions contribute to the etiology of the disease. Therefore, besides lifestyle factors, genetic variations are likely to have a prominent role in the etiology of CHD. The advances of GWAS have made it possible to assess many SNPs across the genome and uncovered SNPs that are associated with CHD and its related risk factor traits. The identification of these SNPs provides a chance to evaluate whether the inclusion of genetic variants could improve risk prediction model performances in addition to phenotypic risk factors. Some studies have tried to integrate genetic factors into the model in European ancestry individuals, including the FHS [166-168]. It was found that adding genetic factors will improve model performance in some of the investigation [166, 168] while others found that the results remained the same [167]. However, similar and systematic studies are lacking in non-European populations, including in Singaporean Chinese.

2.4 Gene-gene and gene-environment interaction studies

As mentioned earlier, CAD as well as its metabolic risk factor traits, specifically referring to as BMI / obesity and HDL in this dissertation, are complex diseases that both genetic, lifestyle factors and their interactions contribute to the etiology of the disease. In the last section of this chapter, research related to gene-gene and gene-environment interaction studies will be reviewed.

2.4.1 Gene-gene interaction study

Gene-gene interaction, also known as epistasis, is the phenomenon that the function of one gene is modified by other gene(s) thus the combined effect of multiple genes is different from their individual effect. Statistically speaking, interaction indicates the departure from a linear model, which describes the relationship between some predictor variable(s) (independent variable) and the outcome variable (dependent variable) [169]. Epistasis can be classified into additivity, magnitude epistasis and sign epistasis. Additivity indicates that there is no interaction exists between genes and the effect of the double mutation is calculated by summing up individual mutation effect together. Magnitude epistasis includes positive epistasis, negative epistasis, synergistic epistasis and antagonistic epistasis. Positive epistasis is that the phenotype of double mutation is fitter than expected from single mutation effects [170, 171]. If both of the mutations are beneficial, when the two mutations present together, the improvement will be larger. If both of the mutations are deleterious, the combination of them will have a protective effect [172]. Negative epistasis is

just the opposite [173, 174]. Synergistic epistasis refers to as the fitness effect of two mutations is more drastic than expected from single effect while antagonistic epistasis is just the opposite [175]. Synergistic epistasis is negative and antagonistic epistasis is positive for deleterious mutations while situation is just the opposite for advantageous mutations. Sign epistasis is the effect of one mutation becoming opposite in the presence of another mutation [176]. The most extreme form of sign epistasis is called reciprocal sign epistasis, which occurs when the effect of two deleterious genes becomes beneficial [177].

The interactions between genes have an essential role both in the function and structure of genetic pathways, as well as the evolutionary dynamics of complex diseases [170]. The motivation of gene-gene interaction investigation for human complex disease is the previous failures to replicate genetic findings in different cohorts and ethnicities. It is believed that the differences between individual genetic effects in different cohorts might be due to fundamental complexity caused by epistasis [178, 179]. Several diseases have been shown to exhibit epistasis, such as type 2 diabetes [180], bipolar effective disorder [181] and CAD [182]. The major limitation of gene-gene interaction studies is the total number of tests conducted, which roughly equals to the square of the number of genes. Stringent significance threshold will be set in order to control false positive findings thus the sample size of such studies usually needs to be very large [183].

2.4.2 Gene-environment interaction study

Gene–environment interaction (G×E) is the phenomenon that different genotypes respond to environmental variation differently. It can lead to different disease phenotypes since the response to the same environmental factors are different in individuals with different genotypes. Gene–environment interaction has two different conceptions, biometric / statistical interaction and developmental / commonsense interaction [184, 185]. The biometric (statistical) conception tries to measure the relative proportions of contributions to phenotypic variation within populations due to genetic and environmental factors while developmental (commonsense) conception commonly used in the area of developmental genetics and developmental psychobiology. Gene-environment interaction studies can also be classified into different types, including synergy, modification and redundancy [186]. The study of gene–environment interactions is important for several reasons. First of all, a better estimation for the proportion of the disease explained by the environment, genes and their combined effect can be gained by conducting such studies (population-attributable risk). Secondly, the association between environmental factors and diseases can be strengthened in genetically susceptible individuals, increasing the probability of identifying true associations. Thirdly, it makes use of information on susceptibility genes to reveal the disease mechanisms and focus on the biological pathways and the environmental factors related to the pathways. Fourthly, it identifies the key compounds leading to the disease from a mixture of compounds that human exposed to. Fifthly, researchers can design new

preventive and therapeutic strategies based on biological pathways information. Lastly, individuals with different genotypes can respond to environmental stimuli differently according to the results from gene-environment interaction studies thus preventive advice can be provided before disease diagnosis [187].

Chapter 3: Study populations and methods

This thesis is focused on the genetic epidemiology of CAD and its risk factors in Singaporean Chinese who are mainly the second or third generation migrants from the southeastern coastal provinces of China (Fujian, Guangdong and Hainan). It is the largest ethnic group in Singapore, constituting 76.2% of Singaporean citizens in 2014 (http://www.nptd.gov.sg/portals/0/news/population-in-brief-2014.pdf). In this chapter, detailed information regarding the Chinese cohorts, anthropometric and laboratory measurements, genotyping and quality control of SNPs and samples in these study populations that were involved in our multiple studies will be described.

3.1 Study populations

3.1.1 Singapore Chinese Health Study (Study II, III and IV)

The Singapore Chinese Health Study (SCHS) is a population-based long term prospective study focused on the effect of dietary intake, genetic factors and environmental components on cancer and other chronic diseases in Singapore [188]. A total of 63,257 Chinese individuals aged between 45-74 years (mean age 56.5), were recruited into SCHS from April 1993 to December 1998. Participants of the study were restricted to Chinese individuals from two major dialect groups in Singapore, the Cantonese, who were originally from Guangdong Province and the Hokkiens, who originated from southern Fujian Province. The study subjects were residing in government-built estates which housed 86% of the Singapore population during the enrolment period. At recruitment, all the study subjects were interviewed

in-person at home by a trained interviewer with a structured questionnaire. In April 1994, a 3% random sample of study subjects was re-contacted for donation of blood specimens and the effort was later extended to include all consenting cohort enrollees, which led to the collection of blood in 28,439 participants by 2001. The study was approved by the Institutional Review Boards (IRB) of the National University of Singapore (NUS) and the University of Minnesota (UMN), and all study subjects gave written informed consent.

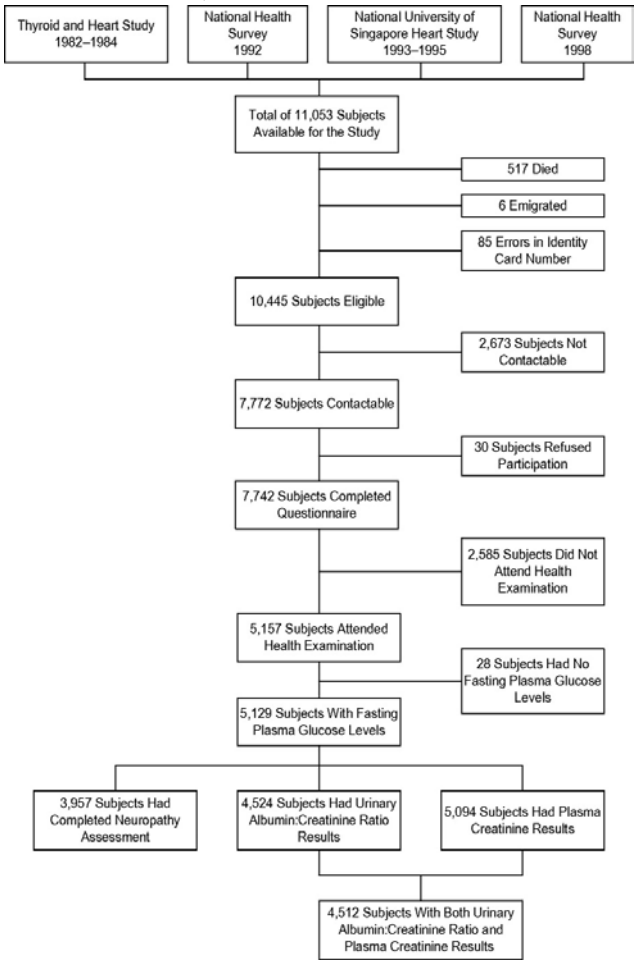
The first round of followed-up interviews was conducted from 1999 to 2004 and the second round was from 2006 to 2010. During the second round follow-up, MI cases (definite MI, probable MI and suspect MI) and CHD death (definite fatal MI, definite fatal CHD and possible fatal CHD) were identified and verified in SCHS from the following three databases: (a) The Singapore Myocardial Infarction Registry (SMIR); (b) A government national hospital discharge database based on inpatient admission and discharge information followed by medical record review by a cardiologist using MI diagnostic criteria from the Multi-Ethnic Study of Atherosclerosis (ICD-9: 410); (c) The Singapore Registry of Births and Deaths (ICD-9: 410–414). For each case, two controls that were alive and free of the disease at the time of the diagnosis or death of the index case were matched to the case on year of recruitment, date of birth, gender, father's dialect group and the date of blood collection. In total, there were 761 incident cases, including 292 CHD death and 1,400 controls (N = 2,161). This subset forms a CAD case-control study nested within the prospective SCHS. In the

subsequent paragraphs, this subset of the cohort is referred to as SCHS.

3.1.2 Singapore Prospective Study Program (Study III and IV)

The Singapore Prospective Study Program (SP2) is a population-based cross-sectional study of adult Singaporean Chinese, Malay and Asian-Indian samples, aged between 24 to 95 years that comprises four previous studies, Thyroid and Heart Study (1982–1984) [189], National Health Survey (1992) [190], National University of Singapore Heart Study (1993–1995) [191], and the National Health Survey (1998) [192] (N = 11,053). Individuals in these studies were sampled randomly from the Singapore population and a disproportionate sampling scheme was utilized to increase the sample sizes of Malays and Asian Indians. After excluding individuals who were either deceased as shown by data linkage to the Registry of Births and Deaths (N = 517), emigrated (N = 6) and had errors in their identity card number (N = 85), there were 10,445 individuals eligible for study. Among these 10,445 subjects, 2,673 were not contactable and 30 (0.3%) refused to participate. Thus 7,742 individuals (response rate: 74.1%) completed the questionnaire and 5,157 of them (66.6% of individuals with completed questionnaire) attended the subsequent clinical examination. The flow chart for inclusion of subjects in SP2 has been described previously in other studies [193] (Figure 2). The study was approved by the IRB of NUS and the Singapore General Hospital. All participants gave informed written consent before the study.

Figure 2: Flow chart of study subjects exclusion in the Singapore Prospective Study Program (Nang, Khoo et al. 2009)



3.1.3 Singapore Chinese Eye Study (Study IV)

The Singapore Chinese Eye Study (SCES) is an ongoing population-based cross-sectional study of adult Singaporean Chinese aged 40 years old and above. The study was conducted from February 2009 and the study subjects were residing in the southwestern part of Singapore. SCES shared the same study protocol with the Singapore Malay Eye Study (SiMES) [194] and the Singapore Indian Eye Study (Sindi) [195]. The ethnicity of study subjects were established from a census list and verified using national identification cards and questionnaire [196]. Participants were selected on the basis of an age-stratified random sampling strategy with a list

provided by the Ministry of Home Affairs. In total, 4,605 individuals were eligible to participate, and subsequently 3,353 participants were recruited (response rate: 72.8%). The study was approved by the IRB of the Singapore Eye Research Institute. All participants gave written informed consent.

3.2 Anthropometric and laboratory measurements

3.2.1 Singapore Chinese Health Study

At recruitment, all the study subjects were interviewed in-person by a trained interviewer at home with a structured questionnaire. Cigarette smoking, history of diabetes and use of antihypertensive medication were self-reported during the interview. SBP was measured by trained doctors and nurses after the participants were seated at rest for at least 5 minutes (mins) using Omron Automatic Digital Blood Pressure Monitors (HEM 705CP) three times with a 3-min interval between each measurement according to validated standard procedures [197]. The average value of the three readings was calculated.

The blood samples from 28,439 participants were kept on ice during transport immediately after collection. They were then separated into various components (plasma, serum, red blood cells and buffy coat) and moved into -80°C freezer for long-term storage [198].

Non-fasting total cholesterol concentration was measured based on an enzymatic

method, utilizing cholesterol esterase and cholesterol oxidase conversion [199] by using the Siemens Advia 2400 instrument. HDL concentration was measured according to the method of Izawa et al [200]. Concentration of hsCRP was measured by particle enhanced immunoturbidimetric assay using Roche Cobas Intergra 400 plus (Roche Diagnostics, Rotkreuz, Switzerland). Creatinine was measured by creatininase (Siemens Advia 2400) and hemoglobin A1c (HbA1c) was measured by cation-exchange high-performance liquid chromatography (HPLC, Biorad Variant II) [201, 202]. The within-batch coefficient of variations (CVs) were as follow: total cholesterol (0.5-1.5%), HDL (0.6-0.7%), hsCRP (0.5-2.3%), creatinine (0.6-1.1%) and HbA1c (0.9-1.0%). The between-batch CVs were as follow: total cholesterol (1.0-1.3%), HDL (1.2-3.5%), hsCRP (0.9-3.5%), creatinine (0.3-1.8%) and HbA1c (0.0-1.0%) [203].

3.2.2 Singapore Prospective Study Program

Detailed information on demography and use of anti-hypertensive medication was collected by using interviewer-administered questionnaires.

As mentioned above, among 7,742 individuals who completed the questionnaire, 5,157 of them attended the subsequent clinical examination. Venous blood was drawn and collected after the participants were fasted overnight for 10 hours. All biochemical analyses were performed at the National University Hospital Referral Laboratory. Plasma concentration of total cholesterol and HDL were measured by

an automated autoanalyzer (ADVIA 2400; Bayer Diagnostics, Tarrytown, New York). The intraday CVs for total cholesterol and HDL were 0.80%-1.57% and 0.56%-0.65%, respectively. The interday CVs for total cholesterol and HDL were 0.93%-1.15% and 1.18%-2.00% respectively [204].

3.2.3 Singapore Chinese Eye Study

All study subjects were examined at the Singapore Eye Research Institute. Data on demography and use of anti-hypertensive medication was collected by using interviewer-administered questionnaires [205].

Non-fasting venous blood sample (40ml) was collected for biochemistry tests. Plasma concentration of total cholesterol and HDL were measured by using turbidimetric inhibition immuno assays with Roche-Cobas® CE analyser (Roche Diagnostics, Germany) [206].

3.3 Genotyping and quality control

GWAS is an investigation of common genetic variants (mainly SNPs) in a group of cases and controls to find out whether there is any variant associated with a disease. Genotyping is the process of determining the genetic makeup of an individual. Quality control (QC), which includes SNP QC and sample QC, is an essential procedure to minimize bias and false-positive or false-negative findings in GWAS. SNP QC would remove SNPs that at least had one of the following features: (1) SNPs

with excessive missing genotype (> 5.0%), (2) SNPs with significant departure from Hardy-Weinberg Equilibrium (HWE, $P < 10^{-6}$-10^{-4}), (3) SNPs with significantly different missingness in cases and controls, and (4) monomorphic SNPs or SNPs with very low minor allele frequency (MAF, < 1.0%). Sample QC would remove individuals that had at least one of the following features: (1) individuals with discordant information on gender, (2) individuals with excessive heterozygosity or missing of genotypes, (3) duplicates (monozygotic twins) or related individuals (first-degree relatives), (4) individuals with divergent ancestry or discordant ethnic information [118].

3.3.1 Singapore Chinese Health Study

A total of 2,161 individuals from SCHS were genotyped on Illumina ZHONGHUA Bead 8 Array version 1 (900,015SNPs) (San Diego, California, the United States). According to sample QC described above, 158 individuals were excluded due to low sample call rate (< 98.0%, N = 35), excessive heterozygosity (beyond the range of mean ± 3 standard deviation (SD), N = 20), related samples (monozygotic duplicates: N = 42; first-degree relatives: N = 25), discordant ethnicity (N = 2), and outliers identified by principle components analysis (N = 34). After exclusion, there were 2003 individuals (719 incident cases and 1,284 controls) left for the following analysis. Among the 900,015 SNPs on the chip, 895,493 of them passed genotype calling algorithms. We further excluded 24,461 non-autosomal SNPs, 467 low call rate SNPs (< 95.0%), 435 SNPs that significantly departed from HWE ($P_{HWE} < 10^{-6}$),

67,585 SNPs with low MAF (< 1.0%) and 1 SNP without strand information. In total, 802,634 SNPs passed SNP QC procedure. Detailed information on SNP and sample QC in SCHS is presented in Table 2.

Table 2: Quality check of Single Nucleotide Polymorphisms and samples in the Singapore Chinese Health Study

SNP QC	
	Number of exclusion (N)
Non-autosomal SNPs	24,461
Low call rate (< 95.0%)	467
Departure from Hardy-Weinberg Equilibrium in controls ($P_{HWE} < 10^{-6}$)	406
Low minor allele frequency (< 1.0%)	67,524
SNP without strand information	1
Number of SNPs remained	802,634
Sample QC	
Low call rate (< 98.0%)	35
Excessive heterozygosity (beyond the range of mean ± 3 standard deviation)	20
Monozygotic duplicate	42
First-degree relative	25
Discordant ethnicity	2
Second-degree relatives	17
Population outlier	17
Number of individuals remained	2003

3.3.2 Singapore Prospective Study Program

Among 5,157 individuals who were both completed the questionnaire and attended the subsequent clinical examination, 3,236 of them were Chinese ancestry. A total of 3,066 Chinese were genotyped on three different Illumina arrays (San Diego, California, the United States): Illumina 1Mduov3 (SP21m, N = 1,016), HumanHap 610Quad (SP2610, N = 1,467) and HumanHap550 (SP2550, N = 583). Since SP2550 was relatively small, only SP2610 and SP21m were included in the subsequent studies. Based on sample QC procedure, 272 individuals were excluded

due to low call rate and excessive heterozygosity (N = 22), relatedness (N = 226), discordant ethnic membership (N = 17) or discrepancy of information on gender between the genetically inferred and clinically recorded (N = 7) [207]. The number of SNPs covered by HumanHap 610Quad and 1Mduov3 was 620,881 and 1,185,068 respectively [208]. In SP2610, we excluded 20,431 non-autosomal SNPs, 48,765 SNPs with low call rate (< 95.0%), 53 SNPs that had significant departure from HWE ($P_{HWE} < 10^{-4}$) and 49,596 SNPs with low MAF (< 1.0%). In SP21m, the number of SNPs excluded due to the same criteria with SP2610 was 48,765, 192,334, 122 and 101,791, respectively. Another 62 SNPs were further removed due to allelic discrepancies between chips. Detailed information on SNP and sample QC in SP2 is presented in Table 3.

3.3.3 Singapore Chinese Eye Study

In total, 1,952 individuals from SCES were genotyped on the HumanHap 610Quad array. According to sample QC, 63 individuals were excluded due to low call rate and excessive heterozygosity (N = 14), relatedness (N = 41), discordant ethnic membership (N = 6) or discrepancy in genders (N = 2) [207]. After exclusion, 1,889 individuals were available for analysis. A total of 87,891 autosomal SNPs were excluded due to low call rate (N = 26,437), monomorphism or low MAF (N = 59,633) or significantly deviating from HWE ($P_{HWE} < 10^{-6}$, N = 1,821). Detailed information on SNP and sample QC in SCES is presented in Table 4.

Table 3: Quality check of Single Nucleotide Polymorphisms and samples in the Singapore Prospective Study Program

SNP QC		
	Number of exclusion (N)	
	610	1M
Non-autosomal SNPs	20,431	48,765
Low call rate (< 95.0%)	48,765	192,334
Departure from Hardy-Weinberg Equilibrium in controls ($P_{HWE} < 10^{-4}$)	53	122
Low minor allele frequency (< 1.0%)	49,596	101,791
SNP with allelic discrepancies between chips	62	
Number of SNPs remained	492,579	841,994
Sample QC		
Low call rate (< 98.0%) and excessive heterozygosity (beyond the range of mean ± 3 standard deviation)	10	12
Cryptic relationship	193	33
Population outlier	10	7
Gender mismatch	3	4
Number of individuals remained	1146	953

Table 4: Quality check of Single Nucleotide Polymorphisms and samples in the Singapore Chinese Eye Study

SNP QC	
	Number of exclusion (N)
Low call rate (< 95.0%)	26,437
Departure from Hardy-Weinberg Equilibrium in controls ($P_{HWE} < 10^{-6}$)	1,821
Monomorphism or low minor allele frequency (< 1.0%)	59,633
Number of SNPs remained	492,108
Sample QC	
Low call rate (< 98.0%) and excessive heterozygosity (beyond the range of mean ± 3 standard deviation)	14
Cryptic relationship	41
Population outlier	6
Gender mismatch	2
Number of individuals remained	1889

3.4 Imputation

Genotype imputation is a mathematical approach that can predict unobserved genotypes by using known haplotypes in a population based on high LD. It could

largely increase the number of SNPs studied and power of the analysis.

3.4.1 Singapore Chinese Health Study

In SCHS, additional autosomal SNPs were imputed with IMPUTE v2 [125]. Genotype calls were based on HapMap East-Asian samples that were derived from Han Chinese from Beijing (CHB) and the Japanese in Tokyo (JPT). A posterior probability of no less than 0.90, a call rate of no less than 95.0 % and info score more than 0.50 were applied to all imputed SNPs. SNP QC was conducted separately in CAD cases and controls. In cases, SNPs were excluded due to low MAF (N = 207,426), significantly departed from HWE ($P_{HWE} < 10^{-5}$, N = 278), low call rate (N = 433,049), low info score (N = 9) and 1,169,467 imputed SNPs were left for analysis. In controls, SNPs were excluded due to low MAF (N = 206,201), significantly departed from HWE (PHWE < 10^{-5}, N = 794), low call rate (N = 426,042), low info score (N = 5) and 1,177,187 imputed SNPs passed QC [209]. The information regarding SCHS SNP QC is displayed in Table 5.

3.4.2 Singapore Prospective Study Program

In SP2, imputation was conducted by using IMPUTE v0.5.0 [125] for all study subjects to maximize the information available. Genotype calls were based on the phased haplotypes in Phase 2 release 22 of the International HapMap Project (HapMap2 r22) East-Asian samples (CHB + JPT) [207, 208]. Actual genotyped calls were replaced back and a call rate of no less than 95.0 % and a posterior probability of no less than 0.90 were applied to all imputed SNPs. In SP2610, SNPs

were excluded due to low MAF (N = 189,571), significantly departed from HWE ($P_{HWE} < 10^{-4}$, N = 392,044), low call rate (N = 1,668), low info score (N = 6) and 1,342,046 imputed SNPs were left for analysis. In SP21m, SNPs were excluded due to low MAF (N = 153,908), significantly departed from HWE (PHWE < 10^{-4}, N = 225,135), low call rate (N = 761), low info score (N = 4) and 1,229,818 imputed SNPs passed QC [208]. The information regarding SP2 SNP QC is displayed in Table 6.

Table 5: Quality check of imputed Single Nucleotide Polymorphisms in the Singapore Chinese Health Study

	MI cases	MI controls
Low minor allele frequency (< 1.0%)	207,426	206,201
Departure from Hardy-Weinberg Equilibrium ($P_{HWE} < 10^{-5}$)	278	794
Low call rate (< 95.0%)	433,049	426,042
Low info score (< 0.50)	9	5
Number of SNPs remained	1,169,467	1,177,187

Table 6: Quality check of imputed Single Nucleotide Polymorphisms in the Singapore Prospective Study Program

	610	1M
Low minor allele frequency (< 1.0%)	189,571	153,908
Departure from Hardy-Weinberg Equilibrium ($P_{HWE} < 10^{-4}$)	392,044	225,135
Low call rate (< 95.0%)	1,668	761
Low info score (< 0.50)	6	4
Number of SNPs remained	1,342,046	1,229,818

Chapter 4: The genetic variation rs6903956 in the novel *ADTRP* gene is not associated with levels of plasma coagulation factors in the Singaporean Chinese

4.1 Introduction

CAD is one of the most important causes of mortality and morbidity in both developed and developing countries [5], with men having higher disease risk than women of a given age [7, 210]. In 2013, it resulted in 8.14 million deaths (16.8%) compared to 5.74 million deaths (12%) in 1990 [2]. CAD occurs when atherosclerosis develops and plaques form to narrow and block the coronary arteries. Patients may not be aware of it for decades until a sudden heart attack finally arises, which brings a heavy disease burden to the public health system and the individuals. CAD is a complex disease and its susceptibility is contributed by genetic and lifestyle components (smoking, diet and physical inactivity) as well as their interactions.

With the recent rapid development of genotyping technologies, GWAS have increasingly been used to identify susceptibility loci for complex diseases. Several novel susceptibility loci have also been reported for CAD thus far, including rs6903956 in the *C6orf105* region of chromosome 6p24.1, which was specifically identified in the Chinese population. The minor risk allele A of rs6903956 was found to be associated with reduced mRNA expression of *C6orf105* and increased risk of CAD [46]. This region was later found to code for a novel transmembrane protein which could regulate mRNA expression, cellular distribution and

anticoagulant activity of tissue factor pathway inhibitor (TFPI), both in native conditions and in response to androgen. Thus the novel protein has been named androgen-dependent TFPI regulating protein (ADTRP). It was further reported that a decreased expression of ADTRP resulted in the reduction of mRNA expression of TFPI. Therefore, ADTRP is postulated to have an anti-coagulating effect [108].

TFPI is a known inhibitor of coagulation, as it reversibly inhibits Factor Xa (FXa) and also tissue factor-factor VIIa (TF-FVIIa) complex in the presence of FXa. TF-FVIIa complex is the main initiator of the extrinsic coagulation cascade in cardiovascular disease [211]. Tissue factor (TF) is normally found on the outside of blood vessels and not exposed to the blood. Once injury occurs, TF is exposed to the bloodstream and binds to circulating FVII [212, 213]. FVII will be then rapidly converted to the activated form (FVIIa), which binds factor X (FX) and results in its conversion to activated FX (FXa), leading eventually to thrombin activation. Thrombin converts soluble fibrinogen to insoluble fibrin strands and form blood clots [213-215]. Previous studies have shown that coagulation factors have an essential role in advancing atherosclerosis and CAD [49-51]. High levels of FVII coagulant activity (FVIIc) and fibrinogen have been found to be significantly associated with increased risk of coronary events [52].

Previously, the association between rs6903956 within the first intron of *ADTRP* and risk for CAD was replicated in our Singaporean Chinese population [47]. The study

also found that the association was not mediated through plasma lipid levels. As ADTRP has been found to up-regulate TFPI, we hypothesized that it is likely to have an impact on key coagulation factors, such as FVIIc and fibrinogen, which are known to have an association with CAD risk. The effect of the genetic variant in *ADTRP* on CAD might thus be due to its impact on plasma FVII and fibrinogen levels. This study was conducted to investigate the effect of the rs6903956 variant on FVIIc and fibrinogen levels in both Singaporean Chinese adults and neonates.

4.2 Method

4.2.1 Study population

To determine the impact of the *ADTRP* genetic variant on plasma FVIIc and fibrinogen, we conducted the analysis in a group of healthy subjects who were free from CAD at the time of recruitment. In total, 421 adult subjects were included in the analysis. The participants were volunteers who underwent regular medical examination at a health screening center in the community. The participants were excluded from the study if they suffered from (1) hypertension, (2) CAD, (3) diabetes, (4) had abnormal ECG. All the study subjects were required to fill in a questionnaire which included the following information: age, height, weight, race, cigarette smoking history, oral contraceptives usage, medical history and family history. Body mass index (BMI) was calculated as weight in kilograms (kg) divided by height in meter square (m^2).

The neonatal subjects involved in our study were recruited from consecutive healthy Chinese newborn babies who were delivered at the National University Hospital in Singapore. The following groups of subjects were excluded from the analysis: (1) babies of mixed heritage; (2) parents with vague information on family or medical history; (3) premature babies with less than 37 weeks of gestational age or less than 2500 grams of birth weight; (4) babies who needed medical treatment or observation in the neonatal ward for had perinatal problems, and those with major congenital deformities, or known or suspected chromosomal syndromes; (5) mothers with recognized medical problems before pregnancy, or gestational conditions such as diabetes or pregnancy-induced hypertension [216]. A total of 1,267 neonates were recruited from the three major ethnic groups in Singapore and of these, 447 of Chinese ethnicity with available FVIIc, fibrinogen and rs6903956 genotype information were included in our analysis.

This study was carried out in accordance with the Declaration of Helsinki for experiments involving humans and was approved by the Hospital's Domain Specific Review Board. All adult subjects gave consent for their participation and for neonates, informed consent was sought from either of their parents.

4.2.2 Blood collection

Details of the blood collection procedures were reported previously for the adult [217] and neonatal populations [218]. Briefly, blood samples for the adult study were

collected after subjects had fasted overnight for at least 10 hours while the neonatal samples were obtained from umbilical cords. Plasma was separated within 3 hours from blood collection tubes that were anti-coagulated with sodium citrate. The plasma was aliquoted into three cryotubes, immediately snap-frozen in liquid nitrogen and stored at -70°C until use. The analyses were performed within 4 weeks of storage. Packed cells were stored at -20°C for the purpose of extraction of genomic DNA.

4.2.3 Measurement of coagulation factors

FVIIc was estimated by a one-stage semiautomatic bioassay in an H Amelung coagulometer at 37°C [219]. FVIIc can activate FX in the presence of tissue thromboplastin and calcium. FVII deficient plasma will have a greatly prolonged prothrombin time (PT). When FVII deficient plasma were mixed with the test plasma, the degree of correction of the PT is proportional to the level of plasma FVII of the participants.

Fibrinogen was measured using the von Clauss assay [220] in the H Amelung coagulometer. Soluble fibrinogen, in the presence of excess bovine thrombin, can be converted into insoluble fibrin and thus clot is formed. The clotting time obtained is inversely proportional to the concentration of fibrinogen.

4.2.4 Genotype determination

Genotype was determined by the polymerase chain reaction restriction fragment length polymorphism method (PCR–RFLP). A 409 base pairs (bp) amplicon of the *ADTRP* gene was amplified from genomic DNA (forward primer: 5′CTTCAACACTTGGGGGACCAACCTTAAGTATTAA3′ and reverse primer: 5′AATAGTTAAGTGTATTTCTGACTCCACGTTGCTG3′). The DNA sequence of the *ADTRP* was obtained from National Center for Biotechnology Information (NCBI) dbSNP database (build 37). The amplification reactions were performed using T-Gradient Thermocyclers (Biometra) in a 20-μL mixture (1 × QIAGEN buffer, 10 pmol of forward primer, 10 pmol of reverse primer, 200 μM of dNTP each, 0.5U of QIAGEN Taq DNA polymerase and 1 μL of the DNA template). The PCR conditions were initial denaturation at 95°C for 4 minutes (Step 1), denaturation at 94°C for 30 seconds (Step 2), annealing at 64°C for 45 seconds (Step 3), extension at 72°C for 1 minute (Step 4) and a final extension of 72°C for 5 minutes (Step 5). Step 2-4 were repeated for 29 cycles before step 5 was executed. The resultant PCR products were digested with *ASeI* in the thermal cycler at 37°C for 16 hours and at 65°C for 20 minutes to heat inactivate the restriction enzyme. The digested products were run on 3% agarose gel [47]. The presence of 2 DNA fragments with the length of 378 and 31 bp respectively indicated the presence of the minor risk A allele while a single band of 409 bp indicated the presence of the major G allele. A total of 6 random selected samples including two samples each for the three different genotypes were confirmed by Sanger sequencing. Another 20 random samples were also

sequenced and all 26 samples had 100% concordance for genotypes obtained from both methods.

4.2.5 Statistical analysis

Among all the study subjects recruited, 309 adults and 447 neonates had complete information for both genotypes and coagulation factor measurements, thus data from these participants were included in the analysis.

Quantitative variables were presented as mean ± SD (standard deviation) while categorical variables were presented as number of individuals (percentage %). Analysis was carried out in adults and neonates separately. FVIIc and fibrinogen levels were not normally distributed in both adults and neonates. Hence, they were both Z-score transformed for subsequent analysis. Pearson's χ^2 test was also used to check whether genotype frequencies significantly departed from Hardy–Weinberg expectations (HWE). Linear regression was used to investigate the association between rs6903956 and Z-score transformed coagulation factors. In adults, age, BMI, gender and cigarette smoking status were included into the model as covariates while in neonates, gender, gestational age and birth weight were included as covariates. All statistical analyses were carried out using STATA 12.0 (Stata Corp, College station, TX) and a 5% type I error was set to indicate statistical significance (two-tailed) in all analyses.

4.3 Results

The main demographic and clinical characteristics of adult and neonatal study subjects are summarized in Table 7 and Table 8, respectively.

Table 7: Descriptive characteristics of adult study subjects

	N = 309
Age (years)	34.95 ± 12.34
BMI (kg/m^2)	22.16 ± 3.55
Gender (Male %)	154(49.84%)
FVIIc (%)	114.28±36.53
Fibrinogen (mg/dl)	276.45 ±64.78
Cigarette Smoking	
never	258(84.04%)
ever	4(1.30%)
current	45(14.66%)
rs6903956	
GG	278(89.97%)
GA	31(10.03%)

Data was presented as Mean ± Standard Deviation (SD) or N (%).

Table 8: Demographics of the Chinese neonatal subjects

	N = 447
Gestational age (weeks)	39.15 ± 1.21
Birth weight (g)	3253.05 ± 355.33
Gender (Male %)	215 (48.10%)
FVIIc (%)	59.73 ± 18.31
Fibrinogen (mg/dl)	128.73 ± 53.40
rs6903956	
GG	390 (87.25%)
GA	57 (12.75%)

Data was presented as Mean ± Standard Deviation (SD) or N (%).

The observed genotype frequencies of rs6903956 did not depart significantly from HWE in both adults (p = 0.353) and neonates (p = 0.150). The homozygous genotype for the minor allele A was absent in both cohorts. The MAF of rs6903956 was 5.0% and 6.4% respectively for adults and neonates, which is similar to the MAF previously reported in Han Chinese and Japanese population [46].

Table 9 shows the association between coagulation factors and rs6903956 on *ADTRP* in adult and neonate population. In adults, levels of FVIIc and fibrinogen were not found to be significantly impacted by rs6903956 after adjusting for the confounding effects of age, gender, BMI and cigarette smoking status (P for FVIIc = 0.464; P for fibrinogen = 0.349). The association was also not significant in the neonates after adjusting for gestational age, gender and birth weight (P for FVIIc = 0.579; P for fibrinogen = 0.359).

Table 9: Genotypic coagulation factors levels of rs6903956 in the Chinese adult and neonatal population

	Adults			Neonates		
	GG (N = 278)	GA (N = 31)	P*	GG (N = 390)	GA (N = 57)	P*
FVIIc	108.60 (36.00, 226.00)	108.00 (46.00, 160.00)	0.464	55.65 (25.99, 184.70)	54.24 (31.40, 150.70)	0.579
Fibrinogen	266.35 (4.00, 584.26)	274.00 (62.44, 434.92)	0.349	132.53 (43.49, 260.30)	147.80 (46.11, 271.70)	0.359

Data was presented as Median (Min, Max).
*The association between genotype and z-score transformed coagulation factors were tested by linear regression adjusting for possible confounders.

4.4 Discussion

The formation of arterial thrombi induced by ruptured atherosclerotic plaques plays a central role in the development of CAD [221]. The exposure of a thrombogenic surface in the ruptured plaque triggers platelet activation and coagulation, which further promotes thrombosis in the coronary arteries. The coagulation system consists of a series of procoagulant and anticoagulant proteins which are present in circulation [222]. In vivo, the exposure of TF to the circulating blood initiates activation of the extrinsic coagulation cascade. It binds to FVII on the cell surface and the TF-FVII complex activates Factor IX (FIX) and FX. FXa converts

prothrombin to thrombin and then thrombin activates platelets and converts fibrinogen to fibrin. FVII plays a central role in initiating the process of coagulation in conjunction with TF while fibrinogen is essential for forming the final fibrin clot [223, 224]. Both FVII and fibrinogen were reported to be independent risk predictors for CAD [223, 225-227]. Several anticoagulant systems operate at the same time of coagulation to regulate procoagulant activity [222]. One of the important anticoagulants is TFPI, which inactivates both FVIIa and FXa, thus inhibiting the extrinsic coagulation pathway [228].

In 2011, Wang et al. [46] first showed that rs6903956, which is located in intron 1 of the *C6orf105* region, on chromosome 6p24.1 was associated with CAD risk in Han Chinese population. The mRNA expression of *ADTRP* gene was significantly lower in individuals with AA and AG genotypes compared to those with GG genotypes. Subsequently, this region has been reported by another group that encodes a gene for a androgen-dependent protein that could regulate the mRNA expression, cellular distribution and anticoagulant activity of TFPI [108]. It is suggested that a decreased expression of *ADTRP* may lead to a reduction in TFPI expression and thus result in an increased risk for atherosclerosis and CAD. The association between rs6903956 and CAD risk has been replicated in independent Chinese cohorts [47, 107]. This SNP was also reported to be associated with CAD in the Japanese, although the risk allele in their population was G and hence different from the Chinese [48]. This SNP has not been found to be associated with CAD in the

European populations [89].

Previously, our group replicated the association between rs6903956 and CAD risk in the Singaporean Chinese and found that plasma lipids such as HDL cholesterol, LDL cholesterol and triglycerides failed to explain the association [47]. Under the influence of androgen, ADTRP has been found to up-regulate TFPI [108]. This has downstream effects on FVII and fibrinogen, both of which are known to be associated with increased CAD risk [52]. In this study, we investigated whether there is any association between rs6903956 and two coagulation factors, FVII and fibrinogen. No significant association between the SNP and the two coagulation factors was observed in the adults and neonates. We tested for the association in the neonatal cohort as we assumed that the effect of any genetic factors could be observable at birth. Our group had previously shown that variation of FVIIc levels at birth could be significantly determined by genetic factors such as polymorphisms in the FVII gene [216]. Hence, determination of the potential impact of the ADTRP variant was extended to the neonatal population. One advantage of studying genetic effects in the neonates is that the confounding effects of environmental factors could be minimized as these can be challenging to tease apart in adult studies.

As there is no prior report on the effect of the *ADTRP* genetic variants on coagulation factor levels, we are unable to estimate the sample size require for such a study to be adequately powered. The post analysis power estimates from this study is 15.12%

for FVIIc and 28.16% for fibrinogen. Given the very small effect sizes observed in this study, a sufficiently large sample size to detect a statistically significant impact of rs6903956 on FVIIc and fibrinogen is estimated to be 7,000. With such a large sample size required, it is unlikely that there is any notable impact of this SNP on these two coagulation factors.

In conclusion, we found that despite the *ADTRP* gene being involved in the regulation of TFPI, its genetic variant rs6903956 is not associated with plasma FVIIc and fibrinogen levels.

Chapter 5: Utility of genetic and non-genetic risk factors in predicting Coronary Heart Disease in Singaporean Chinese

5.1 Introduction

CHD and its complication, MI are leading causes of mortality and morbidity worldwide [5]. In Asia, there is an increasing CHD burden due to rising prevalence of sedentary lifestyle and changes in food consumption [11, 12]. CHD is a chronic disease and the atherosclerotic process begins long before disease onset. Many contributing risk factors modulate the probability of developing CHD. Being able to identify individuals who are apparently healthy but are at high risk of developing CHD would be important for implementing early intervention and treatment.

A number of risk prediction methods have been developed to identify an individual's risk of CHD by means of known risk factors, such as the Framingham Risk Equation, SCORE and QRISK [152, 155, 157, 229, 230]. The most frequently used model is the Framingham Risk Equation, of which the most updated version is based on The Adult Treatment Panel III (Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) [231]. It includes major CHD risk factors, such as age, HDL cholesterol, total cholesterol, SBP, current smoking status and use of anti-hypertensive medication [232]. Although the risk prediction model performed well in multiple cohorts with or without model recalibration [160, 164, 165, 233], it is suggested that 50% of individuals with few risk factors and predicted to be at low risk

of developing disease were actually CHD patients [234, 235]. This calls for the need to improve its risk prediction accuracy. Some studies have focused on evaluating whether including other phenotypic risk factors, such as CRP could improve prediction performance, but the results thus far have been controversial [53-55, 203].

Besides lifestyle factors, genetic variations are likely to have a prominent role in the etiology of CHD as the heritability of CHD is estimated to be up to 60% [18-20]. The advances of GWAS have made it possible to assess many SNPs across the genome and uncovered SNPs that are associated with CHD and its related risk factor traits. The identification of these SNPs provides a chance to evaluate whether the inclusion of genetic variants could improve risk prediction model performances in addition to phenotypic risk factors. Since the reported effect sizes of individual SNPs have been modest, a combined Genetic Risk Score (GRS) containing multiple SNPs should be considered instead to evaluate the role of all identified common variants in aggregate.

In this study, we evaluated whether the inclusion of GRS could improve the prediction accuracy of incident 'hard' CHD (myocardial infarction and coronary death) beyond the use of phenotypic risk factors, which include conventional risk factors from ATPIII model as well as other biomarkers, such as hsCRP and creatinine. We sought to do this by comparing the discrimination and risk reclassification of the

models with and without GRS in a Singaporean Chinese population.

5.2 Method

5.2.1 Study population

We used data from a case-control study (N = 2161; 761 cases and 1400 controls) nested within the SCHS, which is a long term prospective study focused on dietary, genetic and environmental determinants of cancer and other chronic diseases in Singapore [188]. Detailed information regarding SCHS was described in chapter 3.

5.2.2 Outcome of the study

The outcome of the study was 'hard' CHD, which includes myocardial infarction and coronary heart disease death. Cases and controls were selected from participants who donated blood and were free of coronary heart disease or stroke at the time of blood collection. Study subjects were followed up until 31 December 2010. The incident cases of CHD were identified from the following three databases: (a) The SMIR; (b) A governmental national hospital discharge database based on inpatient admission and discharge information followed by medical record review by a cardiologist using MI diagnostic criteria from the Multi-Ethnic Study of Atherosclerosis; (c) The Singapore Registry of Births and Deaths. For each case, two controls who were alive and free of coronary heart disease at the time of the diagnosis or death of the index case were matched to the case on year of recruitment, date of birth, gender, father's dialect group and the date of blood collection.

Detailed information on the selection of participants is described previously in Chapter 3.

5.2.3 Examination and laboratory measures

Baseline information on age, current smoking status, diabetes, SBP and use of anti-hypertensive medication were obtained at recruitment. Current smoking status, history of diabetes and use of anti-hypertensive medication were self-reported and obtained by participant interview. SBP was measured three times with a 3-min interval between each measurement after the participants were seated at rest for at least 5 min, according to validated standard procedures [197]. The average value of the three readings was used for analysis. Details of the procedures of blood collection, processing and storage for SCHS, as well as the analysis for the plasma biomarkers (total cholesterol, HDL cholesterol, hsCRP, creatinine and HbA1c) have been described previously in Chapter 3.

5.2.4 Subset for statistical analysis

Since the original ATPIII model is intended for individuals free of CHD and its risk equivalent, we excluded from our analysis subjects who were diabetic (either reported prior history of diabetes or level of hbA1c > 6.5%), with high level of hsCRP (> 10 mg/L) or high level of serum creatinine (> 600 umol/L). After exclusion, there were 441 cases and 1052 controls available for the statistical analysis.

5.2.5 SNP selection and construction of GRS

All SNPs included in the GRS were reported previously in the Catalog of Published GWAS [78] (https://www.ebi.ac.uk/gwas/) and were associated with CHD, MI or CHD risk factors, including HDL cholesterol, LDL cholesterol, triglycerides, diabetes, fasting glucose related traits, blood pressure, obesity, BMI and CRP. Each SNP was coded as 0, 1 or 2 for common allele homozygous, heterozygous and risk allele homozygous, respectively.

The construction of GRS can be carried out by a simple summation of risk allele that each individual carries or in a more sophisticated manner by weighting each risk allele with its effect size from the GWAS publication ($\sum$ weight × SNP). In order to compare whether there was a significant difference between unweighted and weighted GRS regarding their contribution to the improvement of model performance, a small set of SNPs (10 SNPs) was used to construct both the unweighted and weighted GRS. The 10 SNPs included in these two GRS met the following criteria: (1) associated with CHD or MI; (2) genotyped in SCHS; (3) the risk alleles were consistent in GWAS publications and in SCHS. The range of the unweighted and weighted GRS is 10.00 (4.00, 17.00) and 10.39 (3.36, 17.62) for men and 10.00 (4.00, 16.00) and 10.55 (3.36, 16.68) for women, respectively. Detailed information about the SNPs included in the unweighted and weighted GRS is presented in Table 10.

After the comparison between weighted and unweighted GRS, four GRS were simply generated as a count of risk alleles. Two GRS included only SNPs that were

Table 10: SNPs included in the unweighted and weighted Genetic Risk Score (GRS)

	SNP	Region	Reported Gene(s)	Mapped gene	Reported risk allele	Reported p-value	Weight
1	rs974819	11q22.3	PDGFD	MTND1P36 - MIR4693	T	2.00E-09	0.07
2	rs4380028	15q25.1	ADAMTS7, MORF4L1	ADAMTS7 - TRNAK6	C	4.00E-09	0.07
3	rs3729639	16q22.1	LCAT	E2F4; EXOC3L1	T	2.00E-11	0.09
4	rs17465637	1q41	MIA3	MIA3	C	1.00E-08	0.13
5	rs2259816	12q24.31	HNF1A,C12orf43	HNF1A	T	5.00E-07	0.08
6	rs9268402	6p21.32	C6orf10, BTNL2	C6orf10	G	3.00E-15	0.15
7	rs9349379	6p24.1	PHACTR1	PHACTR1	G	2.00E-09	0.14
8	rs11556924	7q32.2	ZC3HC1	ZC3HC1	C	9.00E-18	0.09
9	rs4977574	9p21.3	CDKN2A, CDKN2B	CDKN2B-AS1	G	1.00E-22	0.25
10	rs579459	9q34.2	ABO	ABO - SURF6	C	4.00E-14	0.10

reported to be associated with CHD or MI (18-SNPs and 13-SNPs) while the other two contained SNPs associated with CHD and its risk factors (156-SNPs and 51-SNPs). Two different selection criteria were used. The first only included SNPs that have been reported to be robustly associated with the outcome ($P < 5\times10^{-8}$) in at least two independent cohorts (18-SNPs and 156-SNPs). The risk alleles of these SNPs were consistent in GWAS and in SCHS. The second selection method used the Cox proportional hazards models with adjustments for age and gender to evaluate all the SNPs retrieved from the GWAS catalog. Those associated with p values less than 0.10 in our dataset were used to build the GRS (13-SNPs and 51-SNPs). In men, the GRS are 18 (range: 10-26) for 18-SNPs; 12 (range: 6-19) for 13-SNPs; 126 (range: 100-148) for 156-SNPs and 48 (range: 35-60) for 51-SNPs. In women, the GRS are 18 (range: 9-24) for 18-SNPs; 12 (range: 5-20) for 13-SNPs; 126.5 (range: 104-144) for 156-SNPs and 48 (range: 35-63) for 51-SNPs.

Genome-wide genotyping and HapMap imputation data for 836 male (267 cases and 569 controls) and 470 female (128 cases and 342 controls) SCHS samples were available for analysis and these methods have been described previously in Chapter 3. All SNPs used to construct the GRS had high call-rate (>95%), had genotype proportions that did not depart significantly from Hardy-Weinberg expectations and were uncorrelated ($r^2 < 0.2$) with each other. Detailed information about the SNPs included in the GRS is presented in Table 11.

5.2.6 Risk prediction models

To assess the effect of the GRS on risk prediction for 'hard' CHD, we considered adding the GRS to three different base models. The first one (M_1) is the recalibrated ATPIII model. In this model, we used the regression coefficients from the FHS (https://www.framinghamheartstudy.org/risk-functions/coronary-heart-disease/hard-10-year-risk.php) and replaced the Framingham mean values of the risk factors and average incidence rate with those estimated from the SCHS study. The second base model (M_2) included all predictors and interaction terms from the ATPIII model but with the regression coefficients estimated using SCHS data. The third base model (M_3) included hsCRP and creatinine as risk factors in the model in addition to all predictors from the ATPIII model. Creatinine and hsCRP were log transformed for men and used as quadratic term for women [203] in M_3. The comparison between different risk prediction models is presented in Table 12.

Table 11: SNPs included in the Genetic Risk Score (GRS)

	SNP	GRS	Region	Disease/Trait	Reported Gene(s)	Mapped gene	SNP source	Reported risk allele	Reported p-value
1	rs10923931	156-SNPs/51-SNPs	1p12	Type 2 diabetes	*NOTCH2, ADAM30*	*NOTCH2*	Imputation	T	4.00E-08
2	rs12740374	18-SNPs/156-SNPs	1p13.3	CHD	*CELSR2, PSRC1, SORT1*	*CELSR2*	Imputation	T	2.00E-42
3	rs7542900	51-SNPs	1p21.3	Type 2 diabetes	*SLC44A3, F3*	*F3 - KATNBL1P2*	Genotype	C	6.00E-06
4	rs1514177	156-SNPs	1p31.1	Obesity	*TNNI3K*	*TNNI3K;FPGT-TNNI3K*	Imputation	C	5.00E-09
5	rs2815752	156-SNPs	1p31.1	BMI	*NEGR1*	*RPL31P12 - KRT8P21*	Genotype	A	2.00E-22
6	rs1748195	156-SNPs	1p31.3	Triglycerides	*ANGPTL3*	*DOCK7*	Genotype	C	2.00E-10
7	rs4420065	156-SNPs	1p31.3	CRP	*LEPR*	*LEPR - PDE4B*	Genotype	C	4.00E-62
8	rs17367504	156-SNPs	1p36.22	SBP	*MTHFR, NPPA, CLCN6, NPPB, AGTRAP*	*MTHFR*	Genotype	G	2.00E-16
9	rs267733	156-SNPs	1q21.3	LDL	*ANXA9, CERS2*	*ANXA9*	Genotype	G	5.00E-09
10	rs4537545	156-SNPs	1q21.3	CRP	*IL6R*	*IL6R*	Genotype	T	2.00E-14
11	rs7553007	156-SNPs	1q23.2	CRP	*CRP*	*CRP - RPL27P2*	Genotype	A	8.00E-44
12	rs543874	156-SNPs	1q25.2	BMI	*SEC16B*	*BRINP2 - SEC16B*	Genotype	G	4.00E-23
13	rs1689800	156-SNPs	1q25.3	HDL	*ZNF648*	*LOC100130996*	Imputation	G	5.00E-20
14	rs17465637	18-SNPs/156-SNPs	1q41	CHD	*MIA3*	*MIA3*	Genotype	C	1.00E-08
15	rs10489615	156-SNPs	1q42.13	HDL	*GALNT2*	*GALNT2*	Genotype	G	4.00E-09
16	rs12239046	51-SNPs	1q44	CRP	*NLRP3*	*NLRP3*	Imputation	C	1.00E-15
17	rs6029526	156-SNPs	20q12	LDL	*TOP1*	*TOP1*	Imputation	A	5.00E-18
18	rs6102059	156-SNPs	20q12	LDL	*MAFB*	*LOC102724968*	Imputation	T	4.00E-09
19	rs1800961	156-SNPs	20q13.12	HDL	*HNF4A*	*HNF4A*	Genotype	T	2.00E-34
20	rs4812829	156-SNPs	20q13.12	Type 2 diabetes	*HNF4A*	*HNF4A*	Imputation	A	5.00E-08
21	rs7679	156-SNPs/51-SNPs	20q13.12	HDL	*PLTP*	*PCIF1*	Genotype	C	4.00E-09
22	rs13041126	156-SNPs	20q13.2	Obesity	*MRPS33P4*	*ERP29P1 - MRPS33P4*	Imputation	T	2.00E-08
23	rs2836878	51-SNPs	21q22.2	CRP	*PSMG1*	*RPSAP64 - RPL23AP12*	Genotype	G	2.00E-07
24	rs243021	156-SNPs/51-SNPs	2p16.1	Type 2 diabetes	*BCL11A*	*RNA5SP94 - MIR4432*	Genotype	A	3.00E-15

Table 11 (continued): SNPs included in the Genetic Risk Score (GRS)

	SNP	GRS	Region	Disease/Trait	Reported Gene(s)	Mapped gene	SNP source	Reported risk allele	Reported p-value
25	rs1561288	156-SNPs	2p23.3	BMI	*POMC*	*EFR3B*	Imputation	T	5.00E-08
26	rs780092	156-SNPs	2p23.3	Triglycerides	*GCKR*	*GCKR*	Genotype	G	5.00E-27
27	rs12713956	156-SNPs	2p24.1	LDL	*APOB*	*APOB*	Genotype	G	4.00E-08
28	rs1367117	156-SNPs	2p24.1	LDL	*APOB*	*APOB*	Genotype	A	1.00E-182
29	rs2867125	156-SNPs	2p25.3	BMI	*TMEM18*	*FAM150B - TMEM18*	Genotype	C	3.00E-49
30	rs4854307	51-SNPs	2p25.3	BMI	Intergenic	*FAM150B - TMEM18*	Genotype	C	2.00E-06
31	rs6734238	156-SNPs	2q13	CRP	*IL1F10*	*IL1F10 - IL1RN*	Imputation	G	2.00E-17
32	rs7560163	156-SNPs	2q23.3	Type 2 diabetes	*RBM43, RND3*	*RND3 - FABP5P10*	Imputation	C	7.00E-09
33	rs13002573	156-SNPs	2q24.3	BP	*FIGN*	*FIGN - PRPS1P1*	Imputation	G	2.00E-08
34	rs11891401	51-SNPs	2q24.3	BP	*FIGN, GRB14*	*PRPS1P1 - GRB14*	Imputation	T	2.00E-06
35	rs6725887	18-SNPs/13-SNPs/156-SNPs/51-SNPs	2q33.2	CHD	*WDR12*	*WDR12*	Imputation	C	1.00E-09
36	rs824931	51-SNPs	2q36.1	BMI	*NR*	*RPL23P5 - HSPA9P1*	Imputation	G	3.00E-06
37	rs2972146	156-SNPs	2q36.3	HDL	*IRS1*	*NYAP2 - MIR5702*	Imputation	G	2.00E-17
38	rs4607103	156-SNPs	3p14.1	Type 2 diabetes	*ADAMTS9*	*ADAMTS9-AS2*	Genotype	C	1.00E-08
39	rs2535633	156-SNPs	3p21.1	BMI	*ITIH4*	*ITIH4*	Imputation	G	2.00E-10
40	rs2013208	156-SNPs	3p21.31	HDL	*RBM5*	*RBM5*	Genotype	T	9.00E-12
41	rs1717027	156-SNPs	3p22.1	BP	*ULK4*	*ULK4*	Imputation	T	5.00E-13
42	rs7640978	156-SNPs	3p22.3	LDL	*CMTM6*	*CMTM6*	Genotype	T	1.00E-08
43	rs7612463	156-SNPs	3p24.3	Type 2 diabetes	*UBE2E2*	*UBE2E2*	Genotype	C	7.00E-09
44	rs7651039	13-SNPs/51-SNPs	3p25.1	CHD	Intergenic	*BTD*	Genotype	C	2.00E-06
45	rs1801282	156-SNPs	3p25.2	Type 2 diabetes	PPARG	*PPARG*	Genotype	C	6.00E-10
46	rs6805251	156-SNPs	3q13.33	HDL	GSK3B	*GSK3B*	Imputation	T	1.00E-08
47	rs419076	156-SNPs/51-SNPs	3q26.2	BP	MECOM	*MECOM*	Imputation	T	2.00E-13
48	rs7630877	51-SNPs	3q26.33	Type 2 diabetes	PEX5L	*PEX5L*	Genotype	A	7.00E-06
49	rs4402960	156-SNPs	3q27.2	Type 2 diabetes	IGF2BP2	*IGF2BP2*	Genotype	T	9.00E-16

Table 11 (continued): SNPs included in the Genetic Risk Score (GRS)

	SNP	GRS	Region	Disease/Trait	Reported Gene(s)	Mapped gene	SNP source	Reported risk allele	Reported p-value
50	rs13130484	156-SNPs	4p12	BMI	*GNPDA2*	*PRDX4P1 - PRKRIRP9*	Genotype	T	6.00E-09
51	rs4458523	156-SNPs	4p16.1	Type 2 diabetes	*WFS1*	*WFS1*	Genotype	G	2.00E-09
52	rs6815464	156-SNPs	4p16.3	Type 2 diabetes	*MAEA*	*MAEA*	Imputation	C	2.00E-20
53	rs6831256	156-SNPs	4p16.3	Triglycerides	*LRPAP1*	*DOK7*	Genotype	G	2.00E-12
54	rs1458038	156-SNPs	4q21.21	BP	*FGF5*	*PRDM8 - FGF5*	Genotype	T	2.00E-23
55	rs3822072	156-SNPs	4q22.1	HDL	*FAM13A*	*FAM13A*	Imputation	A	4.00E-12
56	rs2602836	156-SNPs	4q23	HDL	*ADH5*	*LOC100507053*	Imputation	A	5.00E-08
57	rs13139571	156-SNPs/51-SNPs	4q32.1	DBP	*GUCY1A3, GUCY1B3*	*GUCY1A3*	Imputation	C	2.00E-10
58	rs1842896	18-SNPs/156-SNPs	4q32.1	CHD	*GUCY1A3*	*MTND1P22 - UCY1A3*	Imputation	T	1.00E-11
59	rs1173766	156-SNPs	5p13.3	BP	*NPR3*	*NPR3 - RPS8P8*	Imputation	C	2.00E-08
60	rs1421811	51-SNPs	5p13.3	BP	*NPR3*	*NPR3*	Imputation	G	2.00E-07
61	rs6450176	156-SNPs	5q11.2	HDL	*ARL15*	*ARL15*	Genotype	A	7.00E-10
62	rs702634	156-SNPs/51-SNPs	5q11.2	Type 2 diabetes	*ARL15*	*ARL15*	Genotype	A	7.00E-09
63	rs12916	156-SNPs	5q13.3	LDL	*HMGCR*	*HMGCR*	Genotype	C	8.00E-78
64	rs4457053	156-SNPs/51-SNPs	5q13.3	Type 2 diabetes	*ZBED3*	*ZBED3-AS1*	Genotype	G	3.00E-12
65	rs261967	156-SNPs/51-SNPs	5q15	BMI	*PCSK1*	*PCSK1 - CAST*	Imputation	C	8.00E-13
66	rs4530754	156-SNPs	5q23.2	LDL	*CSNK1G3*	*CSNK1G3*	Imputation	G	4.00E-12
67	rs4705952	156-SNPs	5q31.1	CRP	*IRF1*	*IRF1 - IL5*	Genotype	G	1.00E-08
68	rs987237	156-SNPs	6p12.3	BMI	*TFAP2B*	*TFAP2B*	Genotype	G	3.00E-20
69	rs6905288	13-SNPs/51-SNPs	6p21.1	CHD	*VEGFA*	*TRNAI25*	Imputation	T	7.00E-08
70	rs9470794	156-SNPs	6p21.2	Type 2 diabetes	*ZFAND3*	*ZFAND3*	Imputation	C	2.00E-10
71	rs2254287	156-SNPs	6p21.32	LDL	*B3GALT4*	*COL11A2*	Genotype	G	5.00E-08
72	rs9268402	18-SNPs/156-SNPs	6p21.32	CHD	*C6orf10, BTNL2*	*C6orf10*	Genotype	G	3.00E-15
73	rs805303	156-SNPs	6p21.33	DBP	*BAT2, BAT5*	*BAG6*	Genotype	G	3.00E-11
74	rs1799945	156-SNPs	6p22.2	DBP	*HFE*	*HFE*	Genotype	G	2.00E-15

Table 11 (continued): SNPs included in the Genetic Risk Score (GRS)

	SNP	GRS	Region	Disease/Trait	Reported Gene(s)	Mapped gene	SNP source	Reported risk allele	Reported p-value
75	rs3757354	156-SNPs	6p22.3	LDL	*MYLIP*	*MYLIP*	Genotype	T	2.00E-17
76	rs7756992	156-SNPs	6p22.3	Type 2 diabetes	*CDKAL1*	*CDKAL1*	Genotype	G	8.00E-09
77	rs9349379	18-SNPs/13-SNPs/156-SNPs/51-SNPs	6p24.1	CHD	*PHACTR1*	*PHACTR1*	Genotype	G	2.00E-09
78	rs6901250	156-SNPs	6q22.1	CRP	*GPRC6A*	*GPRC6A*	Genotype	A	5.00E-08
79	rs605066	156-SNPs	6q24.1	HDL	*CITED2*	*CITED2 - ATP5F1P6*	Imputation	C	3.00E-08
80	rs6922269	18-SNPs/156-SNPs	6q25.1	CHD	*MTHFD1L*	*MTHFD1L*	Imputation	A	3.00E-08
81	rs4607517	51-SNPs	7p13	Fasting glucose-related traits	*GCK*	*GCK - YKT6*	Genotype	A	2.00E-16
82	rs17428471	156-SNPs	7p15.2	BP	*EVX1, HOXA*	*RPL35P4 - EIF4HP1*	Imputation	T	2.00E-12
83	rs4722551	156-SNPs	7p15.2	LDL	*MIR148A*	*MIR148A - NFE2L3*	Genotype	C	4.00E-14
84	rs1178979	156-SNPs	7q11.23	Triglycerides	*BAZ1B, BCL7B, TBL2, MLXIPL*	*BAZ1B*	Genotype	A	2.00E-12
85	rs10953541	18-SNPs/156-SNPs	7q22.3	CHD	Intergenic	*BCAP29*	Imputation	C	3.00E-08
86	rs17477177	51-SNPs	7q22.3	BP	*PIK3CG*	*CCDC71L -RNA5SP236*	Genotype	T	2.00E-13
87	rs38855	156-SNPs	7q31.2	Triglycerides	*MET*	*MET*	Genotype	G	2.00E-08
88	rs6467136	156-SNPs	7q32.1	Type 2 diabetes	*GCC1, PAX4*	*ZNF800 - GCC1*	Imputation	G	5.00E-11
89	rs11556924	18-SNPs/156-SNPs	7q32.2	CHD	*ZC3HC1*	*ZC3HC1*	Genotype	C	9.00E-18
90	rs972283	156-SNPs	7q32.3	Type 2 diabetes	*KLF14*	*KLF14 - MIR29A*	Genotype	G	2.00E-10
91	rs10105606	156-SNPs	8p21.3	Triglycerides	*LPL*	*LPL - RPL30P9*	Genotype	C	4.00E-26
92	rs10503669	51-SNPs	8p21.3	HDL	*LPL*	*LPL - RPL30P9*	Imputation	A	4.00E-19
93	rs7819412	156-SNPs	8p23.1	Triglycerides	*XKR6, AMAC1L2*	*XKR6*	Genotype	G	3.00E-08
94	rs10102164	156-SNPs	8q11.23	LDL	*SOX17*	*TRMT112P7 - SEC11B*	Imputation	A	4.00E-11
95	rs2293889	156-SNPs	8q23.3	HDL	*TRPS1*	*TRPS1*	Imputation	T	4.00E-17
96	rs2071518	156-SNPs	8q24.12	BP	*NOV*	*NOV*	Genotype	T	4.00E-09
97	rs2001945	156-SNPs	8q24.13	Triglycerides	Intergenic	*TRIB1 - LINC00861*	Imputation	C	1.00E-20

Table 11 (continued): SNPs included in the Genetic Risk Score (GRS)

	SNP	GRS	Region	Disease/Trait	Reported Gene(s)	Mapped gene	SNP source	Reported risk allele	Reported p-value
98	rs6987702	51-SNPs	8q24.13	LDL	*TRIB1*	*TRIB1 - LINC00861*	Imputation	G	3.00E-06
99	rs10968576	156-SNPs	9p21.1	BMI	*LRRN6C*	*LINGO2*	Genotype	G	3.00E-13
100	rs4977574	18-SNPs/13-SNPs/156-SNPs/51-SNPs	9p21.3	CHD	*CDKN2A, CDKN2B*	*CDKN2B-AS1*	Genotype	G	1.00E-22
101	rs581080	156-SNPs	9p22.3	HDL	*TTC39B*	*TTC39B*	Imputation	G	1.00E-19
102	rs17584499	156-SNPs	9p24.1	Type 2 diabetes	*PTPRD*	*PTPRD*	Genotype	T	9.00E-10
103	rs7034200	51-SNPs	9p24.2	Fasting glucose-related traits	*GLIS3*	*GLIS3*	Genotype	A	1.00E-13
104	rs13292136	51-SNPs	9q21.31	Type 2 diabetes	*CHCHD9*	*KRT18P24 -CHCHD2P9*	Imputation	C	3.00E-08
105	rs4149268	156-SNPs	9q31.1	HDL	*ABCA1*	*ABCA1*	Genotype	C	1.00E-10
106	rs817858	51-SNPs	9q31.2	BMI	*RAD23B*	*RAD23B - HMGN2P32*	Imputation	G	7.00E-06
107	rs579459	18-SNPs/13-SNPs/156-SNPs/51-SNPs	9q34.2	CHD	*ABO*	*ABO - SURF6*	Genotype	C	4.00E-14
108	rs11014166	156-SNPs	10p12.31	DBP	*CACNB2*	*CACNB2*	Imputation	A	1.00E-08
109	rs11257655	156-SNPs	10p13	Type 2 diabetes	*CDC123*	*CDC123 - CAMK1D*	Genotype	T	3.00E-09
110	rs1746048	18-SNPs/156-SNPs	10q11.21	CHD	*CXCL12*	*LINC00841 - CXCL12*	Imputation	C	3.00E-10
111	rs970548	156-SNPs	10q11.21	HDL	*MARCH8, ALOX5*	*Mar-08*	Imputation	C	2.00E-10
112	rs1530440	156-SNPs	10q21.2	DBP	*c10orf107, TMEM26, RTKN2, RHOBTB1, ARID5B*	*C10orf107*	Imputation	T	1.00E-09
113	rs10761731	51-SNPs	10q21.3	Triglycerides	*JMJD1C*	*JMJD1C*	Imputation	T	8.00E-12
114	rs1802295	156-SNPs	10q22.1	Type 2 diabetes	*VPS26A*	*VPS26A*	Genotype	A	4.00E-08
115	rs5015480	156-SNPs	10q23.33	Type 2 diabetes	*HHEX, IDE*	*HHEX - EXOC6*	Genotype	C	1.00E-15
116	rs2068888	51-SNPs	10q23.33	Triglycerides	*CYP26A1*	*CYP26A1 - NIP7P1*	Genotype	A	2.00E-11
117	rs11191580	156-SNPs	10q24.33	BMI	*NT5C2*	*NT5C2*	Imputation	C	4.00E-08
118	rs2255141	156-SNPs	10q25.2	LDL	*GPAM*	*GPAM*	Imputation	A	1.00E-13

Table 11 (continued): SNPs included in the Genetic Risk Score (GRS)

	SNP	GRS	Region	Disease/Trait	Reported Gene(s)	Mapped gene	SNP source	Reported risk allele	Reported p-value
119	rs3817334	156-SNPs	11p11.2	BMI	*MTCH2, NDUFS3, CUGBP1*	*MTCH2*	Imputation	T	2.00E-12
120	rs652722	51-SNPs	11p13	BMI	*PAX6*	*DKFZp686K1684*	Genotype	C	8.00E-08
121	rs6265	156-SNPs	11p14.1	BMI	*BDNF*	*BDNF; BDNF-AS*	Genotype	G	5.00E-10
122	rs381815	156-SNPs	11p15.1	SBP	*PLEKHA7*	*PLEKHA7*	Genotype	T	2.00E-09
123	rs5215	156-SNPs	11p15.1	Type 2 diabetes	*KCNJ11*	*KCNJ11*	Genotype	C	3.00E-11
124	rs11024074	51-SNPs	11p15.1	DBP	*PLEKHA7*	*PLEKHA7*	Genotype	T	1.00E-06
125	rs11042023	156-SNPs	11p15.4	Obesity	*RPL27A*	*TRIM66*	Genotype	C	1.00E-11
126	rs163184	156-SNPs	11p15.4	Type 2 diabetes	*KCNQ1*	*KCNQ1*	Genotype	G	2.00E-14
127	rs2923084	156-SNPs	11p15.4	HDL	*AMPD3*	*CAND1.11*	Genotype	G	5.00E-08
128	rs174546	156-SNPs	11q12.2	HDL	*FADS1, FADS2, FADS3*	*FADS1*	Genotype	T	2.00E-39
129	rs1552224	156-SNPs	11q13.4	Type 2 diabetes	*CENTD2*	*ARAP1*	Genotype	A	1.00E-22
130	rs499974	156-SNPs	11q13.5	HDL	*MOGAT2, DGAT2*	*MOGAT2 - DGAT2*	Genotype	A	1.00E-08
131	rs1387153	156-SNPs	11q14.3	Type 2 diabetes	*MTNR1B*	*RPS3AP42 - MTNR1B*	Genotype	T	8.00E-15
132	rs633185	156-SNPs	11q22.1	SBP	*FLJ32810, TMEM133*	*ARHGAP42*	Imputation	G	1.00E-17
133	rs974819	18-SNPs/156-SNPs	11q22.3	CHD	*PDGFD*	*MTND1P36 - MIR4693*	Genotype	T	2.00E-09
134	rs603446	156-SNPs	11q23.3	Triglycerides	*ZNF259, APOA1, APOC3, APOA4, APOA5, BUD13*	*ZPR1*	Imputation	T	2.00E-86
135	rs2266788	51-SNPs	11q23.3	HDL/TG	*APOA5*	*ZPR1; APOA5*	Genotype	C	5.00E-13
136	rs964184	13-SNPs	11q23.3	CHD	*ZNF259, APOA5, APOA4, APOC3, APOA1*	*ZPR1*	Imputation	G	1.00E-17
137	rs7134375	156-SNPs	12p12.2	HDL	*PDE3A*	*TCP1P3 - PDE3A*	Genotype	A	1.00E-08
138	rs10875976	156-SNPs	12q13.12	Obesity	*LOC144233*	*BCDIN3D-AS1*	Genotype	A	2.00E-10
139	rs2261181	156-SNPs	12q14.3	Type 2 diabetes	*HMGA2*	*RPSAP52*	Genotype	T	4.00E-08

Table 11 (continued): SNPs included in the Genetic Risk Score (GRS)

	SNP	GRS	Region	Disease/Trait	Reported Gene(s)	Mapped gene	SNP source	Reported risk allele	Reported p-value
140	rs7961581	156-SNPs	12q21.1	Type 2 diabetes	*TSPAN8, LGR5*	*TSPAN8 - LGR5*	Genotype	C	1.00E-09
141	rs1495377	51-SNPs	12q21.1	Type 2 diabetes	*NR*	*TSPAN8 - LGR5*	Imputation	G	7.00E-06
142	rs2681492	156-SNPs	12q21.33	SBP	*ATP2B1*	*ATP2B1*	Genotype	T	4.00E-11
143	rs2384550	51-SNPs	12q24.21	DBP	*TBX3, TBX5*	*TBX3 - UBA52P7*	Genotype	A	4.00E-08
144	rs2259816	18-SNPs	12q24.31	CHD	*HNF1A, C12orf43*	*HNF1A*	Genotype	T	5.00E-07
145	rs1727313	156-SNPs	12q24.31	Type 2 diabetes	*MPHOSPH9*	*MPHOSPH9*	Imputation	C	1.00E-08
146	rs7979473	156-SNPs	12q24.31	CRP	*HNF1A*	*HNF1A*	Genotype	A	1.00E-10
147	rs7989336	156-SNPs	13q32.1	Obesity	*HS6ST3*	*HS6ST3*	Imputation	A	1.00E-08
148	rs8017377	156-SNPs	14q12	LDL	*NYNRIN*	*NYNRIN*	Genotype	A	3.00E-15
149	rs7141420	156-SNPs	14q31.1	Obesity	*NRXN3*	*NRXN3*	Genotype	T	1.00E-17
150	rs4983559	156-SNPs	14q32.33	HDL	*ZBTB42, AKT1*	*ZBTB42 - LINC00638*	Genotype	G	1.00E-08
151	rs7403531	156-SNPs	15q14	Type 2 diabetes	*RASGRP1*	*RASGRP1*	Genotype	T	4.00E-09
152	rs2929282	156-SNPs	15q15.3	Triglycerides	*FRMD5*	*FRMD5*	Imputation	T	2.00E-09
153	rs1532085	156-SNPs/51-SNPs	15q21.3	HDL	*LIPC*	*LOC102724766*	Genotype	A	1.00E-188
154	rs2241423	156-SNPs	15q23	BMI	*MAP2K5, LBXCOR1*	*MAP2K5*	Genotype	G	1.00E-18
155	rs6495122	156-SNPs	15q24.1	DBP	*CSK, ULK3*	*CPLX3 - ULK3*	Genotype	A	2.00E-10
156	rs7178572	156-SNPs	15q24.3	Type 2 diabetes	*HMG20A*	*HMG20A*	Imputation	G	2.00E-11
157	rs3825807	18-SNPs/156-SNPs	15q25.1	CHD	*ADAMTS7*	*ADAMTS7*	Imputation	A	1.00E-12
158	rs4380028	18-SNPs/13-SNPs/156-SNPs/51-SNPs	15q25.1	CHD	*ADAMTS7, MORF4L1*	*ADAMTS7 - TRNAK6*	Genotype	C	4.00E-09
159	rs2028299	156-SNPs	15q26.1	Type 2 diabetes	*AP3S2*	*AP3S2;C15orf38-AP3S2*	Genotype	C	2.00E-11
160	rs11649653	156-SNPs	16p11.2	Triglycerides	*CTF1*	*CTF2P*	Genotype	G	3.00E-08
161	rs7498665	156-SNPs	16p11.2	BMI	*SH2B1*	*SH2B1*	Imputation	G	5.00E-11
162	rs12597579	156-SNPs	16p12.3	BMI	*GP2*	*SNRPEP3 - GP2*	Imputation	C	1.00E-08
163	rs2531995	156-SNPs	16p13.3	Obesity	*ADCY9*	*ADCY9*	Genotype	T	4.00E-08

Table 11 (continued): SNPs included in the Genetic Risk Score (GRS)

	SNP	GRS	Region	Disease/Trait	Reported Gene(s)	Mapped gene	SNP source	Reported risk allele	Reported p-value
164	rs11642841	156-SNPs	16q12.2	Type 2 diabetes	*FTO*	*FTO*	Genotype	A	3.00E-08
165	rs6499640	156-SNPs	16q12.2	BMI	*FTO*	*FTO*	Genotype	A	4.00E-13
166	rs12708980	156-SNPs	16q13	HDL	*CETP*	*CETP*	Genotype	C	2.00E-28
167	rs3764261	156-SNPs	16q13	HDL	*CETP*	*HERPUD1 - CETP*	Genotype	A	1E-769
168	rs16965039	13-SNPs/51-SNPs	16q13	CHD	*CETP*	*NLRC5*	Imputation	T	6.00E-07
169	rs3729639	18-SNPs/13-SNPs/156-SNPs/51-SNPs	16q22.1	CHD	*LCAT*	*E2F4; EXOC3L1*	Genotype	T	2.00E-11
170	rs8060686	13-SNPs/51-SNPs	16q22.1	HDL/TG	*EDC4*	*EDC4*	Genotype	T	8.00E-06
171	rs16955379	51-SNPs	16q23.2	Type 2 diabetes	*CMIP*	*CMIP*	Imputation	C	3.00E-07
172	rs623323	51-SNPs	17p13.3	Type 2 diabetes	*NXN*	*RNMTL1 - NXN*	Genotype	T	4.00E-06
173	rs4430796	156-SNPs	17q12	Type 2 diabetes	*HNF1B*	*HNF1B*	Genotype	G	9.00E-10
174	rs12946454	156-SNPs	17q21.31	SBP	*PLCD3, ACBD4, HEXIM1, HEXIM2*	*ACBD4; PLCD3*	Imputation	T	1.00E-08
175	rs46522	18-SNPs/13-SNPs/156-SNPs/51-SNPs	17q21.32	CHD	*UBE2Z, GIP, ATP5G1, SNF8*	*UBE2Z*	Imputation	T	2.00E-08
176	rs7206971	156-SNPs	17q21.32	LDL	*OSBPL7*	*EFCAB13*	Imputation	A	4.00E-09
177	rs4129767	156-SNPs/51-SNPs	17q25.3	HDL	*PGS1*	*PGS1*	Imputation	G	2.00E-11
178	rs7503807	51-SNPs	17q25.3	Obesity	*RPTOR*	*RPTOR*	Genotype	A	2.00E-08
179	rs17697518	51-SNPs	18q12.3	Obesity	*KC6*	*RPL17P45 - KC6*	Imputation	-	7.00E-07
180	rs2156552	156-SNPs	18q21.1	HDL	*LIPG*	*SMUG1P1 - ACAA2*	Imputation	T	2.00E-12
181	rs17782313	156-SNPs	18q21.32	BMI	*MC4R*	*RPS3AP49 - MC4R*	Genotype	C	5.00E-18
182	rs2304130	156-SNPs	19p13.11	Triglycerides	*CILP2, ZNF101*	*ZNF101*	Genotype	G	4.00E-08
183	rs10401969	51-SNPs	19p13.11	LDL	*NCAN, CILP2, PBX4*	*SUGP1*	Genotype	C	2.00E-08
184	rs12979813	156-SNPs	19p13.2	HDL	*LOC55908*	*DOCK6*	Imputation	T	2.00E-09
185	rs7248104	156-SNPs	19p13.2	Triglycerides	*INSR*	*INSR; LOC100996405*	Genotype	A	5.00E-10
186	rs11668477	51-SNPs	19p13.2	LDL	*LDLR*	*SMARCA4 - LDLR*	Genotype	G	2.00E-07

Table 11 (continued): SNPs included in the Genetic Risk Score (GRS)

	SNP	GRS	Region	Disease/Trait	Reported Gene(s)	Mapped gene	SNP source	Reported risk allele	Reported p-value
187	rs3803915	13-SNPs/51-SNPs	19p13.3	BMI	*NR*	*AP3D1 - DOT1L*	Genotype	C	5.00E-06
188	rs11084753	156-SNPs	19q13.11	BMI	*KCTD15*	*KCTD15 - RPS4XP20*	Genotype	G	2.00E-08
189	rs731839	156-SNPs	19q13.11	HDL	*PEPD*	*PEPD*	Genotype	G	3.00E-09
190	rs1160985	156-SNPs	19q13.32	LDL	*APOE*	*TOMM40*	Genotype	C	2.00E-21
191	rs11671664	156-SNPs/51-SNPs	19q13.32	BMI	*GIPR, QPCTL*	*GIPR*	Genotype	G	3.00E-12

HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol (LDL-C), BP: blood pressure; BMI: body mass index; CRP: C-reactive protein; CHD: coronary heart disease; DBP: diastolic blood pressure; SBP: systolic blood pressure

Table 12: Comparison of the risk prediction models

Model	Risk predictors	Coefficients	Advantages	Disadvantages
Recalibrated ATPIII model (M_1)	Traditional risk predictors from ATPIII model	Obtained from Framingham Heart Study	Coefficients are more reliable and demonstrated to be applicable to Asian populations.	Coefficients are not available for hsCRP and creatinine.
ATPIII covariates (M_2)	Traditional risk predictors from ATPIII model	Estimate from SCHS	Coefficients are estimated from the local cohort.	Coefficients were derived from a smaller sample size compared to FHS.
M_2 + hsCRP + creatinine (M_3)	Traditional risk predictors from ATPIII model + hsCRP + creatinine	Estimate from SCHS	Coefficients are estimated from the local cohort. Coefficients for hsCRP and creatinine could also be estimated.	Coefficients were derived from a smaller sample size compared to FHS.

hsCRP: High-sensitive C-reactive protein; ATPIII: Adult Treatment Panel III; SCHS: Singapore Chinese Health Study

5.2.7 Statistical analysis

Selecting only a subset of nested case-control (NCC) study participants would normally be problematic had our statistical analysis used the traditional conditional logistic regression that retain the matched-set property of the case-control pairs because some matched-set will be without case or control in the subset. To overcome this potential problem, we used the pseudo-likelihood approach [236] where the matching sets are 'broken' prior to subset selection and each subject is considered as independent individual with their contribution to the study weighted by the inverse of their probability of being included into the NCC study. In our case, to estimate the absolute risk, we fitted a weighted Cox proportional hazards model to estimate the regression coefficients and baseline hazards in which the sampling weight for each case is one and for controls, is the inverse of the probability of being selected into the nested case-control study. Weighted means and SD were calculated for baseline risk factors in cases and controls separately.

The GRS was added to the Cox's proportional hazards model, which contained all the risk factors and the interaction terms from ATPIII model as a categorical variable by using quartiles as cut-off. To assess whether the addition of the GRS improved the model performance, we evaluated the model discrimination by c-statistic [237] and weighted net reclassification improvement (NRI) index [203] was calculated separately for cases and controls [238] to assess the extent to which adding the GRS re-assigned individuals to risk categories that better reflected their actual outcome.

Among the cases, a shift to higher risk categories is classified as improved reclassification while in controls a shift to lower risk categories is classified as improved reclassification. Individuals were classified into four risk categories according to their estimated 10-year 'hard' CHD risks (0-4.99%; 5-9.99% 10-19.99%; 20% and above) to assess the reclassification. As NRI statistic can be prone to model over-fitting [239], we performed leave-one-out (LOO) cross-validation for NRI index and reported the NRI index using the cross-validated models.

All statistical analyses were performed in R3.2.0 (www.r-project.org). A 5% type I error was set to indicate statistical significance.

5.3 Results

5.3.1 Baseline characteristics of study participants

The baseline characteristics of the subjects included in the analysis are presented in Table 13. Cases were older, had higher levels total cholesterol, systolic blood pressure, hsCRP, creatinine; lower levels of HDL cholesterol, more likely to be smokers and be on anti-hypertensive medication for both men and women. Women had higher HDL cholesterol level and higher total cholesterol level compared to men, but the proportion of smokers was lower. All the GRS were higher among the cases than the controls in both men and women.

Table 13: Characteristics of participants of the Singapore Chinese Health Study nested case control study of coronary heart disease†

	Men (N =836)		Women (N =470)	
	Cases (N= 267)	Controls (N= 569)	Cases (N= 128)	Controls (N= 342)
Age at blood collection (years)	65.57(7.69)	63.00(7.57)	69.19(7.74)	63.00(7.12)
Total cholesterol (mg/dL)	202.21(37.15)	195.61(33.20)	217.89(39.87)	210.56(33.28)
HDL-C (mg/dL)	47.50(9.81)	49.43(11.46)	55.83(12.65)	58.71(12.21)
Systolic blood pressure (mm Hg)	145.69(23.05)	136.64(19.59)	148.71(22.39)	134.16(21.19)
Anti-hypertensive treatment	0.38(0.49)	0.25(0.43)	0.34(0.47)	0.27(0.44)
Current smoking	0.41(0.49)	0.32(0.47)	0.16(0.36)	0.05(0.21)
hsCRP (mg/L)	2.13(2.21)	1.31(1.48)	2.00(2.13)	1.55(1.68)
Serum creatinine (mg/dL)	0.94(0.26)	0.86(0.16)	0.68(0.29)	0.62(0.15)
Genetic Risk Score (unweighted)	10.64(1.91)	10.16(2.00)	10.70(1.74)	10.08(2.14)
Genetic Risk Score (weighted)	10.77(2.29)	10.24(2.34)	10.87(2.10)	10.21(2.59)
Genetic Risk Score (18 SNPs)	18.42(2.44)	17.82(2.41)	18.50(2.36)	17.62(2.43)
Genetic Risk Score (13 SNPs)	12.54(2.18)	11.96(2.00)	12.71(1.99)	11.75(2.26)
Genetic Risk Score (156 SNPs)	128.24(7.41)	124.66(7.19)	128.36(7.51)	125.19(7.11)
Genetic Risk Score (51 SNPs)	50.47(4.06)	47.53(3.98)	50.63(3.92)	47.44(3.99)

† Figures are weighted means (weighted SD), calculated using nested case-control data with inverse of probability of inclusions as sampling weights.
hsCRP: high-sensitivity C-reactive protein

5.3.2 Comparison between unweighted and weighted GRS

We first investigated whether there was a significant difference between unweighted and weighted GRS regarding their contribution to the improvement of model performance. As can be seen in Table 14, there was no obvious difference in c-statistics in all three models and in both men and women. When compared the model with weighted GRS to the model with unweighted GRS, no significant change in NRI index was observed in all situations. The two GRS acted most differently in M_2 in females, the weighted GRS had a net gain of 7.8% (p-value = 0.056) cases being reclassified into higher risk categories. Thus a weighted GRS was not significantly better than an unweighted GRS.

5.3.3 Results for men

5.3.3.1 18-SNPs GRS

Table 15 shows the performance of the various prediction models before and after including the 18-SNPs GRS. The best model was M_3, which included all the predictors from ATPIII model as well as the biomarkers creatinine and hsCRP. The 18-SNPs GRS were strongly associated with incident 'hard' CHD in all three models with various adjustments for the effects of confounding factors such as traditional risk factors, hsCRP and creatinine. Men in the highest quartile of the 18-SNPs GRS (>20) had a higher CHD risk, varying from 1.80-fold for M_3 to 1.93-fold for M_2 than those in the lowest quartile (<17).

Improvements in discrimination were assessed for inclusion of the GRS to the three models predicting risk of 'hard' CHD in men. In all three models, adding the 18-SNPs GRS into the base models slightly improved the c-statistics (Table 15). The largest increase occurred when adding the 18-SNPs GRS to the recalibrated Framingham risk model (M_1). The c-statistic improved from 0.663 to 0.678. The best performing model is M_3, for which the c-statistic reached 0.704 after the inclusion of 18-SNPs GRS.

Table 14: Difference in performance of unweighted and weighted Genetic Risk Score (GRS)

Models	Men			Women		
	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)
M_1: Recalibrated Framingham Risk Model						
M_1 + unweighted GRS	0.677(0.018)	-0.004(0.879)	0.021(0.252)	0.782(0.026)	-0.023(0.631)	0.018(0.499)
M_1 + weighted GRS	0.677(0.018)			0.775(0.026)		
M_2: ATPIII covariates						
M_2 + unweighted GRS	0.685(0.018)	0.004(0.873)	-0.013(0.431)	0.788(0.026)	0.078(0.056)	-0.001(0.958)
M_2 + weighted GRS	0.684(0.018)			0.781(0.026)		
M_3: ATPIII covariates + hsCRP + creatinine						
M_3 + unweighted GRS	0.703(0.018)	-0.045(0.064)	0.001(0.952)	0.784(0.026)	-0.023(0.590)	-0.003(0.865)
M_3 + weighted GRS	0.700(0.018)			0.780(0.026)		

NRI: net reclassification improvement; SE: standard error

hsCRP: high-sensitivity C-reactive protein

Table 15: Performance of various prediction models of coronary heart disease with and without 18-SNPs Genetic Risk Score for men

Models	Quartiles of $GRS_{[Range]}$	Hazard Ratio 95% CI	P-value	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)
M_1: Recalibrated Framingham Risk Model				0.663(0.021)	-	-
M_1 + GRS	$Q1_{[10, 16]}$	1.000	-	0.678(0.018)	0.019(0.569)	-0.031(0.178)
	$Q2_{[17, 18]}$	1.122(0.801, 1.572)	0.503			
	$Q3_{[19, 20]}$	1.425(1.027, 1.978)	**0.034**			
	$Q4_{[21, 26]}$	1.895(1.301, 2.759)	**0.001**			
M_2: ATPIII covariates				0.679(0.018)	-	-
M_2 + GRS	$Q1_{[10, 16]}$	1.000	-	0.687(0.018)	-0.007(0.800)	-0.002(0.904)
	$Q2_{[17, 18]}$	1.135(0.809, 1.594)	0.463			
	$Q3_{[19, 20]}$	1.405(1.010, 1.956)	**0.044**			
	$Q4_{[21, 26]}$	1.934(1.318, 2.837)	**0.001**			
M_3: ATPIII covariates + hsCRP + creatinine				0.695(0.018)	-	-
M_3 + GRS	$Q1_{[10, 16]}$	1.000	-	0.704(0.018)	0.030(0.310)	-0.014(0.519)
	$Q2_{[17, 18]}$	1.109(0.790, 1.557)	0.548			
	$Q3_{[19, 20]}$	1.497(1.072, 2.092)	**0.018**			
	$Q4_{[21, 26]}$	1.797(1.221, 2.644)	**0.003**			

Cl: Confidence Interval; NRI: net reclassification improvement; SE: standard error

hsCRP: high-sensitivity C-reactive protein

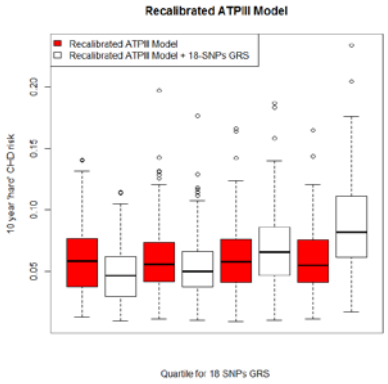
In terms of absolute risk, including 18-SNPs GRS into the base models led to lower absolute risks for individuals in the first two quartiles while predicting higher absolute risks for individuals in the latter two quartiles (Figure 3). This greater separation between individuals in the lower and higher quartiles enabled the new model to identify potential 'hard' CHD cases from the rest of the population. As shown in Table 15, the risk classification was not significantly changed for all three models in both cases and controls. Table 16 shows that the improved reclassification for cases occurs when individuals classified as lower risk group by models without the 18-SNPs GRS were reclassified into the higher risk group by models with the GRS in men.

Table 16: Risk reclassification table (base model with and without 18-SNPs GRS) for male cases of coronary heart disease

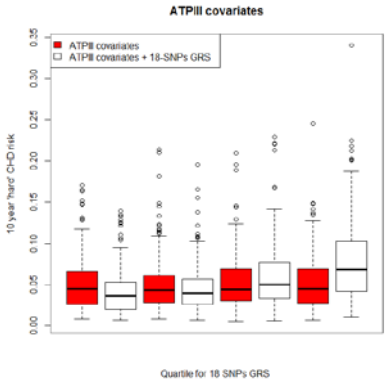
	0-5%	5-10%	10-20%	20% above
M_1: Recalibrated Framingham Risk Model	Recalibrated Framingham Risk Model + 18 SNPs			
0-5%	61	18	0	0
5-10%	25	110	21	0
10-20%	0	11	19	2
20% above	0	0	0	0
M_2: ATPIII covariates	ATPIII covariates + 18 SNPs			
0-5%	107	14	0	0
5-10%	21	75	11	0
10-20%	0	9	22	5
20% above	0	0	2	1
M_3: ATPIII covariates + hsCRP + creatinine	ATPIII covariates + hsCRP + creatinine + 18 SNPs			
0-5%	99	16	0	0
5-10%	20	71	16	0
10-20%	0	7	27	3
20% above	0	0	0	5

hsCRP: high-sensitivity C-reactive protein

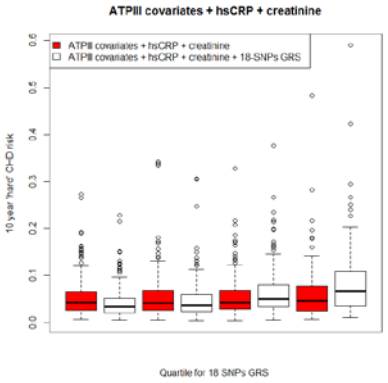
Figure 3: Boxplots of 10-year of coronary heart disease risk estimated using different models with and without 18-SNPs GRS, by quartiles of 18-SNPs GRS in men. (A) Recalibrated Framingham Risk Model (M_1); (B) ATPIII covariates (M_2); (C) ATPIII covariates + hsCRP + creatinine (M_3)



(A)



(B)



(C)

5.3.3.2 13-SNPs GRS

Table 17 shows the performance of the various prediction models before and after including the 13-SNPs GRS. The best model was M_3. The 13-SNPs GRS were strongly associated with incident 'hard' CHD in all three models. Men in the highest quartile of the 13-SNPs GRS (>14) had a higher CHD risk, varying from 2.77-fold for M_1 to 3.07-fold for M_3 than those in the lowest quartile (<12).

Improvements in discrimination were assessed for inclusion of the GRS to the three models predicting risk of 'hard' CHD in men. In all three models, adding the 13-SNPs GRS into the base models improved the c-statistics (Table 17). The largest

Table 17: Performance of various prediction models of coronary heart disease with and without 13-SNPs Genetic Risk Score for men

Models	Quartiles of $GRS_{[Range]}$	Hazard Ratio 95% CI	P-value	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)
M_1: Recalibrated Framingham Risk Model				0.663(0.021)	-	-
M_1 + GRS	$Q1_{[06, 11]}$	1.000	-	0.691(0.018)	0.026(0.468)	0.033(0.166)
	$Q2_{[12, 12]}$	0.916(0.646, 1.300)	0.624			
	$Q3_{[13, 14]}$	1.222(0.902, 1.656)	0.195			
	$Q4_{[15, 19]}$	2.769(1.964, 3.903)	**6.09×10^{-9}**			
M_2: ATPIII covariates				0.679(0.018)	-	-
M_2 + GRS	$Q1_{[06, 11]}$	1.000	-	0.696(0.018)	0.037(0.286)	0.019(0.371)
	$Q2_{[12, 12]}$	0.894(0.627, 1.273)	0.533			
	$Q3_{[13, 14]}$	1.256(0.924, 1.707)	0.145			
	$Q4_{[15, 19]}$	2.874(2.033, 4.064)	**2.27×10^{-9}**			
M_3: ATPIII covariates + hsCRP + creatinine				0.695(0.018)	-	-
M_3 + GRS	$Q1_{[06, 11]}$	1.000	-	0.706(0.018)	**0.087(0.012)**	0.020(0.362)
	$Q2_{[12, 12]}$	0.903(1.108, 1.291)	0.576			
	$Q3_{[13, 14]}$	1.325(0.974, 1.803)	0.074			
	$Q4_{[15, 19]}$	3.074(2.164, 4.366)	**3.58×10^{-10}**			

Cl: Confidence Interval; NRI: net reclassification improvement; SE: standard error

hsCRP: high-sensitivity C-reactive protein

increase occurred when adding the 13-SNPs GRS to the recalibrated Framingham risk model (M_1). The c-statistic improved from 0.663 to 0.691. The best performing model is M_3, for which the c-statistic reached 0.706 after the inclusion of 13-SNPs GRS.

In terms of absolute risk, including 13-SNPs GRS into the base models led to lower absolute risks for individuals in the first two quartiles while predicting higher absolute risks for individuals in the latter two quartiles (Figure 4). As shown in Table 17, the risk classification was improved only in M_3 with a net gain of 8.70% (p-value = 0.012) cases being reclassified into higher risk categories, while it did not significantly reduce the classification accuracy for controls. Table 18 shows that the improved reclassification for cases occurs when individuals classified as lower risk

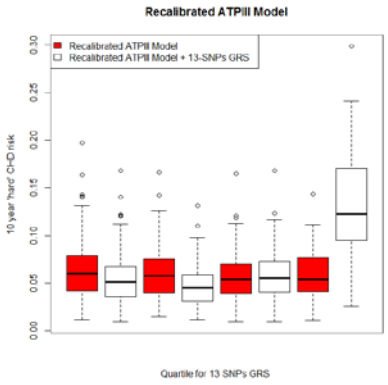
Table 18: Risk reclassification table (base model with and without 13-SNPs GRS) for male cases of coronary heart disease

	0-5%	5-10%	10-20%	20% above
M_1: Recalibrated Framingham Risk Model	Recalibrated Framingham Risk Model + 13 SNPs			
0-5%	61	11	7	0
5-10%	28	101	25	2
10-20%	0	15	12	5
20% above	0	0	0	0
M_2: ATPIII covariates	ATPIII covariates + 13 SNPs			
0-5%	102	16	3	0
5-10%	24	59	22	2
10-20%	0	13	17	6
20% above	0	0	2	1
M_3: ATPIII covariates + hsCRP + creatinine	ATPIII covariates + hsCRP + creatinine + 13 SNPs			
0-5%	101	12	2	0
5-10%	22	58	18	9
10-20%	0	8	17	15
20% above	0	0	0	5

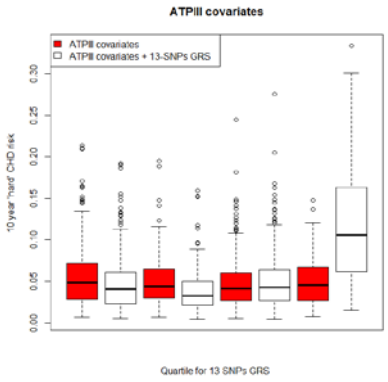
hsCRP: high-sensitivity C-reactive protein

group by models without the 13-SNPs GRS were reclassified into the higher risk group by models with the GRS in men.

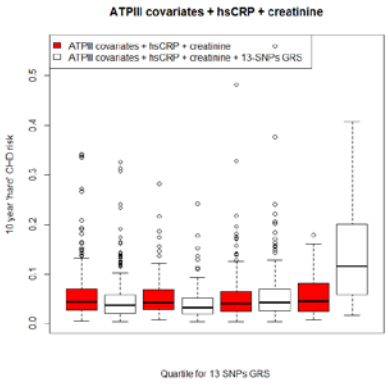
Figure 4: Boxplots of 10-year of coronary heart disease risk estimated using different models with and without 13-SNPs GRS, by quartiles of 13-SNPs GRS in men. (A) Recalibrated Framingham Risk Model (M_1); (B) ATPIII covariates (M_2); (C) ATPIII covariates + hsCRP + creatinine (M_3)



(A)



(B)



(C)

5.3.3.3 156-SNPs GRS

Table 19 shows the performance of the various prediction models before and after including the 156-SNPs GRS. The best model was M_3. The 156-SNPs GRS were strongly associated with incident 'hard' CHD in all three models with various adjustments for the effects of confounding factors. Men in the highest quartile of the 156-SNPs GRS (>131) had a higher CHD risk, varying from 3.54-fold for M_3 to 3.70-fold for M_2 than those in the lowest quartile (<122).

Table 19: Performance of various prediction models of coronary heart disease with and without 156-SNPs Genetic Risk Score for men

Models	Quartiles of $GRS_{[Range]}$	Hazard Ratio 95% CI	P-value	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)
M_1: Recalibrated Framingham Risk Model				0.663(0.021)	-	-
M_1+ GRS	$Q1_{[100,121]}$	1.000	-	0.705(0.018)	**0.124(0.007)**	0.007(0.840)
	$Q2_{[122,126]}$	1.421(0.965,2.095)	0.076			
	$Q3_{[127,131]}$	2.337(1.624,3.363)	**4.81×10^{-6}**			
	$Q4_{[132,149]}$	3.554(2.493,5.065)	**2.35×10^{-12}**			
M_2: ATPIII covariates				0.679(0.018)	-	-
M_2 + GRS	$Q1_{[100,121]}$	1.000	-	0.713(0.018)	**0.176(4.02×10^{-5})**	-0.013(0.659)
	$Q2_{[122,126]}$	1.286(0.866,1.908)	0.212			
	$Q3_{[127,131]}$	2.328(1.614,3.356)	**6.06×10^{-6}**			
	$Q4_{[132,149]}$	3.696(2.587,5.282)	**7.04×10^{-13}**			
M_3: ATPIII covariates + hsCRP + creatinine				0.695(0.018)	-	-
M_3 + GRS	$Q1_{[100,121]}$	1.000	-	0.724(0.018)	**0.159(1.26×10^{-4})**	-0.041(0.167)
	$Q2_{[122,126]}$	1.351(0.907,2.011)	0.138			
	$Q3_{[127,131]}$	2.270(1.568,3.288)	**1.43×10^{-5}**			
	$Q4_{[132,149]}$	3.537(2.463,5.079)	**7.69×10^{-12}**			

Cl: Confidence Interval; NRI: net reclassification improvement; SE: standard error

hsCRP: high-sensitivity C-reactive protein

Improvements in discrimination were assessed for inclusion of the GRS to the three models predicting risk of 'hard' CHD in men. In all three models, adding the 156-SNPs GRS into the base models greatly improved the c-statistics (Table 19). The largest increase occurred when adding the 156-SNPs GRS to the recalibrated Framingham risk model (M_1). The c-statistic improved from 0.663 to 0.705. The best performing model is M_3, for which the c-statistic reached 0.724 after the inclusion of 156-SNPs GRS.

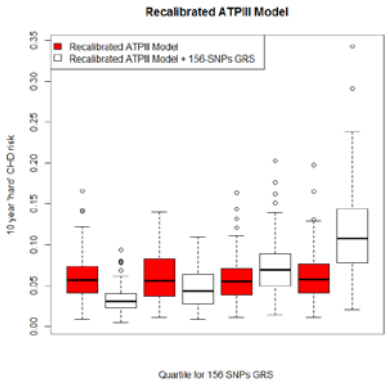
In terms of absolute risk, including 156-SNPs GRS into the base models led to lower absolute risks for individuals in the first two quartiles while predicting higher absolute risks for individuals in the latter two quartiles (Figure 5). As shown in Table 19, the risk classification was improved for all three models with a net gain of cases being reclassified into higher risk categories (NRI index: 12.4% (M_1) - 17.6% (M_2); p-value: 4.02×10^{-5}(M_2) - 0.007 (M_1)), while it did not significantly reduce the classification accuracy for controls. Table 20 shows that the improved reclassification for cases occurs when individuals classified as lower risk group by models without the 156-SNPs GRS were reclassified into the higher risk group by models with the GRS in men.

Table 20: Risk reclassification table (base model with and without 156-SNPs GRS) for male cases of coronary heart disease

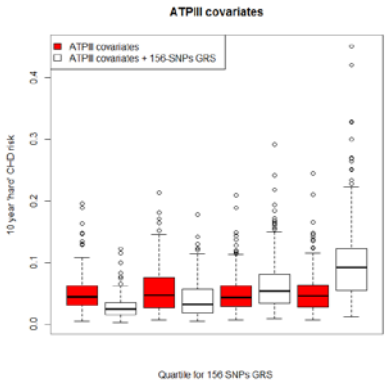
	0-5%	5-10%	10-20%	20% above
M_1: Recalibrated Framingham Risk Model	Recalibrated Framingham Risk Model + 156 SNPs			
0-5%	50	29	0	0
5-10%	42	54	60	0
10-20%	0	16	14	2
20% above	0	0	0	0
M_2: ATPIII covariates	ATPIII covariates + 156 SNPs			
0-5%	83	38	0	0
5-10%	29	39	39	0
10-20%	0	12	12	12
20% above	0	0	1	2
M_3: ATPIII covariates + hsCRP + creatinine	ATPIII covariates + hsCRP + creatinine + 156 SNPs			
0-5%	83	32	0	0
5-10%	31	41	35	0
10-20%	0	8	15	14
20% above	0	0	0	5

hsCRP: high-sensitivity C-reactive protein

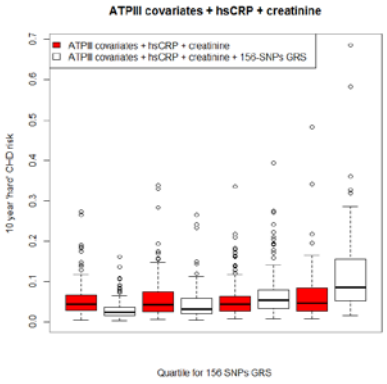
Figure 5: Boxplots of 10-year of coronary heart disease risk estimated using different models with and without 156-SNPs GRS, by quartiles of 156-SNPs GRS in men. (A) Recalibrated Framingham Risk Model (M_1); (B) ATPIII covariates (M_2); (C) ATPIII covariates + hsCRP + creatinine (M_3)



(A)



(B)



(C)

5.3.3.4 51-SNPs GRS

Table 21 shows the performance of the various prediction models before and after including the 51-SNPs GRS. The best model was M_3. The 156-SNPs GRS were strongly associated with incident 'hard' CHD in all three models. Men in the highest quartile of the 51-SNPs GRS (>52) had a higher CHD risk, varying from 3.54-fold for M_3 to 3.70-fold for M_2 than those in the lowest quartile (<46).

Improvements in discrimination were assessed for inclusion of the GRS to the three models predicting risk of 'hard' CHD in men. In all three models, adding the 51-SNPs GRS into the base models extremely improved the c-statistics (Table 21). The largest increase occurred when adding the 51-SNPs GRS to the recalibrated Framingham risk model (M_1). The c-statistic improved from 0.663 to 0.749. The best performing model is M_3, for which the c-statistic reached 0.758 after the inclusion of 51-SNPs GRS.

In terms of absolute risk, including 51-SNPs GRS into the base models led to lower absolute risks for individuals in the first two quartiles while predicting higher absolute risks for individuals in the latter two quartiles (Figure 6). As shown in Table 21, the risk classification was improved for all three models with a net gain of cases being reclassified into higher risk categories (NRI index: 30.3% (M_1) – 39.4% (M_3); p-value: 2.22×10^{-16}(M_3) – 1.14×10^{-9} (M_1)), while it did not significantly reduce the classification accuracy for controls. Table 22 shows that the improved

Table 21: Performance of various prediction models of coronary heart disease with and without 51-SNPs Genetic Risk Score for men

Models	Quartiles of $GRS_{[Range]}$	Hazard Ratio (95% Cl)	P-value	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)
M_1: Recalibrated Framingham Risk Model				0.663(0.021)	-	-
M_1+ GRS	$Q1_{[35, 45]}$	1.000	-	0.749(0.018)	**0.303(1.14 x10^{-09})**	0.034(0.341)
	$Q2_{[46, 48]}$	2.010(1.307,3.092)	**0.001**			
	$Q3_{[49, 52]}$	3.858(2.683,5.548)	**3.15x10^{-13}**			
	$Q4_{[53, 61]}$	7.838(5.389,11.400)	**<2x10^{-16}**			
M_2: ATPIII covariates				0.679(0.018)	-	-
M_2 + GRS	$Q1_{[35, 45]}$	1.000	-	0.753(0.018)	**0.318(4.61 x10^{-12})**	-0.028(0.401)
	$Q2_{[46, 48]}$	2.154(1.396,3.324)	**5.29x10^{-4}**			
	$Q3_{[49, 52]}$	4.145(2.873,5.981)	**2.92x10^{-14}**			
	$Q4_{[53, 61]}$	8.342(5.708,12.190)	**<2x10^{-16}**			
M_3: ATPIII covariates + hsCRP + creatinine				0.695(0.018)	-	-
M_3 + GRS	$Q1_{[35, 45]}$	1.000	-	0.758(0.018)	**0.394(2.22 x10^{-16})**	-0.047(0.156)
	$Q2_{[46, 48]}$	2.497(1.612,3.870)	**4.21x10^{-5}**			
	$Q3_{[49, 52]}$	4.877(3.354,7.094)	**<2x10^{-16}**			
	$Q4_{[53, 61]}$	9.109(6.201,13.380)	**<2x10^{-16}**			

Cl: Confidence Interval; NRI: net reclassification improvement; SE: standard error

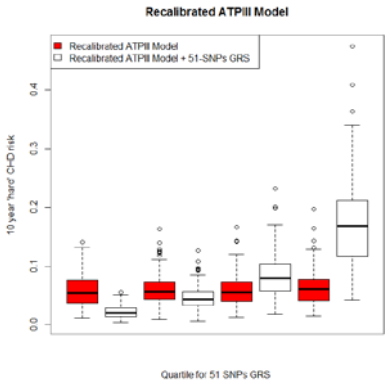
hsCRP: high-sensitivity C-reactive protein

Table 22: Risk reclassification table (base model with and without 51-SNPs GRS) for male cases of coronary heart disease

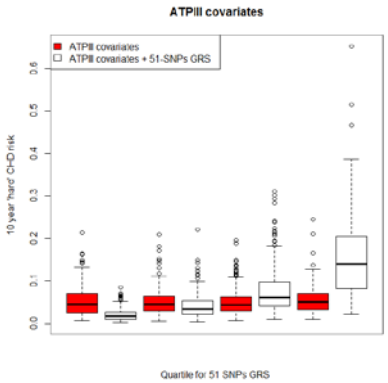
	0-5%	5-10%	10-20%	20% above
M_1: Recalibrated Framingham Risk Model	Recalibrated Framingham Risk Model + 51 SNPs			
0-5%	37	30	12	0
5-10%	37	42	57	20
10-20%	1	10	11	10
20% above	0	0	0	0
M_2: ATPIII covariates	ATPIII covariates + 51 SNPs			
0-5%	71	36	14	0
5-10%	26	29	38	14
10-20%	1	5	14	16
20% above	0	1	0	2
M_3: ATPIII covariates + hsCRP + creatinine	ATPIII covariates + hsCRP + creatinine + 51 SNPs			
0-5%	66	39	10	0
5-10%	24	25	38	20
10-20%	0	2	11	24
20% above	0	1	0	4

hsCRP: high-sensitivity C-reactive protein

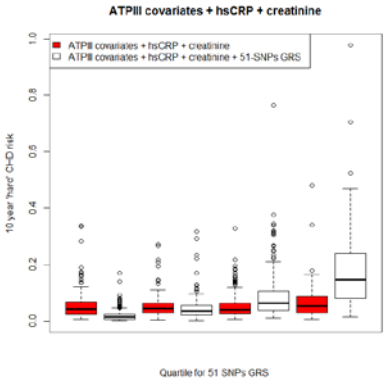
Figure 6: Boxplots of 10-year of coronary heart disease risk estimated using different models with and without 51-SNPs GRS, by quartiles of 51-SNPs GRS in men. (A) Recalibrated Framingham Risk Model (M_1); (B) ATPIII covariates (M_2); (C) ATPIII covariates + hsCRP + creatinine (M_3)



(A)



(B)



(C)

reclassification for cases occurs when individuals classified as lower risk group by models without the 51-SNPs GRS were reclassified into the higher risk group by models with the GRS in men.

5.3.4 Results for women

5.3.4.1 18-SNPs GRS

Table 22 shows the performance of the various prediction models before and after including the 18-SNPs GRS in women. The best model was M_2. The 18-SNPs GRS were strongly associated with incident 'hard' CHD in all three models with different adjustment. Women in the highest quartile of the 18-SNPs GRS (>20) had a higher CHD risk, varying from 4.18-fold in M_1 to 5.28-fold in M_3 than those in the lowest quartile (<17).

Improvements in discrimination were evaluated for the inclusion of the GRS to the three models predicting risk of 'hard' CHD in women. In all three models, adding the 18-SNPs GRS into the base models provided slight improvement in c-statistics (Table 23). The largest increase also occurred when adding the 18-SNPs GRS to M_1, the recalibrated Framingham risk model, the same as in men. The c-statistic increased from 0.765 to 0.775. The c-statistic of the best performing model, M_2, reached 0.782 after adding the 18-SNPs GRS.

Table 23: Performance of various prediction models of coronary heart disease with and without 18-SNPs Genetic Risk Score for women

Models	Quartiles of $GRS_{[Range]}$	Hazard Ratio (95% CI)	P-value	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)
M_1: Recalibrated Framingham Risk Model				0.765(0.026)	-	-
M_1 + GRS	$Q1_{[09, 16]}$	1.000	-	0.775(0.026)	0.078(0.096)	-0.002(0.932)
	$Q2_{[17, 18]}$	1.699(1.003, 2.878)	**0.049**			
	$Q3_{[19, 20]}$	2.158(1.256, 3.709)	**0.005**			
	$Q4_{[21, 25]}$	4.178(2.317, 7.533)	**$2.00x10^{-6}$**			
M_2: ATPIII covariates				0.773(0.026)	-	-
M_2 + GRS	$Q1_{[09, 16]}$	1.000	-	0.782(0.026)	**0.141(0.004)**	-0.023(0.287)
	$Q2_{[17, 18]}$	1.540(0.895, 2.649)	0.119			
	$Q3_{[19, 20]}$	2.081(1.200, 3.607)	**0.009**			
	$Q4_{[21, 25]}$	4.526(2.489, 8.229)	**$7.40x10^{-7}$**			
M_3: ATPIII covariates + hsCRP + creatinine				0.771(0.026)	-	-
M_3 + GRS	$Q1_{[09, 16]}$	1.000	-	0.780(0.026)	**0.102(0.024)**	0.001(0.946)
	$Q2_{[17, 18]}$	1.639(0.938, 2.865)	0.083			
	$Q3_{[19, 20]}$	2.197(1.246, 3.872)	**0.006**			
	$Q4_{[21, 25]}$	5.275(2.856, 9.743)	**$1.08x10^{-7}$**			

Cl: Confidence Interval; NRI: net reclassification improvement; SE: standard error

hsCRP: high-sensitivity C-reactive protein

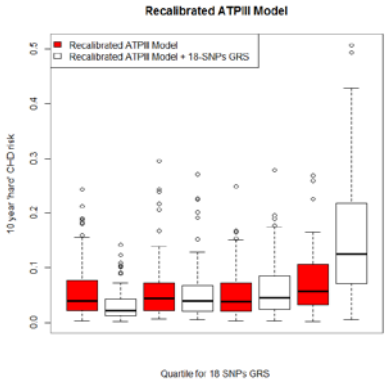
In terms of absolute risk, adding the 18-SNPs GRS into the base models also led to lower absolute risks for individuals in the first two quartiles while higher absolute risks for individuals in the latter two quartiles (Figure 7), which was a similar observation in men. As shown in Table 23, the risk classification was improved for M_2 and M_3 with a net gain of 14.1% (p-value = 0.004) and 10.2% (p-value = 0.024) cases, respectively being reclassified into higher risk categories, while it did not significantly reduce the classification accuracy for controls in these two models. Table 24 shows that the improved reclassification for female cases occurs when individuals classified as lower risk group by models without the 18-SNPs GRS were reclassified into a higher risk group by models with the GRS.

Table 24: Risk reclassification table (base model with and without 18-SNPs GRS) for female cases of coronary heart disease

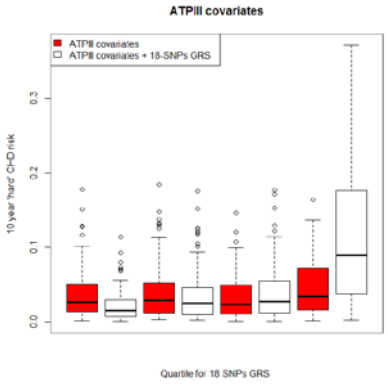
	0-5%	5-10%	10-20%	20% above
M_1: Recalibrated Framingham Risk Model	Recalibrated Framingham Risk Model + 18 SNPs			
0-5%	48	5	1	0
5-10%	8	27	8	1
10-20%	0	5	13	8
20% above	0	0	0	4
M_2: ATPIII covariates	ATPIII covariates + 18 SNPs			
0-5%	74	10	2	0
5-10%	8	14	11	1
10-20%	0	2	2	4
20% above	0	0	0	0
M_3: ATPIII covariates + hsCRP + creatinine	ATPIII covariates + hsCRP + creatinine + 18 SNPs			
0-5%	74	8	4	0
5-10%	7	12	2	3
10-20%	0	2	6	6
20% above	0	0	1	3

hsCRP: high-sensitivity C-reactive protein

Figure 7: Boxplots of 10-year of coronary heart disease risk estimated using different models with and without 18-SNPs GRS, by quartiles of 18-SNPs GRS in women. (A) Recalibrated Framingham Risk Model (M_1); (B) ATPIII covariates (M_2); (C) ATPIII covariates + hsCRP + creatinine (M_3)



(A)



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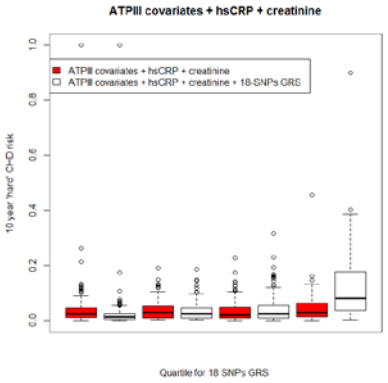


(C)

5.3.4.2 13-SNPs GRS

Table 25 shows the performance of the various prediction models before and after including the 13-SNPs GRS in women. The 13-SNPs GRS were strongly associated with incident 'hard' CHD in all three models with different adjustment. Women in the highest quartile of the 13-SNPs GRS (>20) had a higher CHD risk, varying from 3.63-fold in M_1 to 3.88-fold in M_3 than those in the lowest quartile (<17).

Improvements in discrimination were evaluated for the inclusion of the GRS to the three models predicting risk of 'hard' CHD in women. In all three models, adding

Table 25: Performance of various prediction models of coronary heart disease with and without 13-SNPs Genetic Risk Score for women

Models	Quartiles of $GRS_{[Range]}$	Hazard Ratio (95% CI)	P-value	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)
M_1: Recalibrated Framingham Risk Model				0.765(0.026)	-	-
M_1 + GRS	$Q1_{[09, 16]}$	1.000	-	0.791(0.026)	**0.133(0.024)**	-0.011(0.737)
	$Q2_{[17, 18]}$	1.705(0.983, 2.959)	0.058			
	$Q3_{[19, 20]}$	2.597(1.591, 4.240)	**1.36×10^{-4}**			
	$Q4_{[21, 25]}$	3.626(2.291, 5.738)	**3.83×10^{-8}**			
M_2: ATPIII covariates				0.773(0.026)	-	-
M_2 + GRS	$Q1_{[09, 16]}$	1.000	-	0.798(0.026)	**0.156(0.003)**	-0.005(0.848)
	$Q2_{[17, 18]}$	1.750(0.994, 3.082)	0.052			
	$Q3_{[19, 20]}$	2.707(1.643, 4.460)	**9.22×10^{-5}**			
	$Q4_{[21, 25]}$	3.786(2.372, 6.043)	**2.39×10^{-8}**			
M_3: ATPIII covariates + hsCRP + creatinine				0.771(0.026)	-	-
M_3 + GRS	$Q1_{[09, 16]}$	1.000	-	0.798(0.026)	**0.141(0.007)**	0.014(0.612)
	$Q2_{[17, 18]}$	1.660(0.932, 2.954)	0.085			
	$Q3_{[19, 20]}$	2.864(1.728, 4.745)	**4.44×10^{-5}**			
	$Q4_{[21, 25]}$	3.883(2.417, 6.237)	**2.03×10^{-8}**			

Cl: Confidence Interval; NRI: net reclassification improvement; SE: standard error

hsCRP: high-sensitivity C-reactive protein

the 13-SNPs GRS into the base models provided great improvement in c-statistics (Table 25). The largest increase also occurred when adding the 13-SNPs GRS to M_3, which included all the predictors from ATPIII model as well as the biomarkers creatinine and hsCRP. The c-statistic increased from 0.771 to 0.798.

In terms of absolute risk, adding the 13-SNPs GRS into the base models also led to lower absolute risks for individuals in the first two quartiles while higher absolute risks for individuals in the latter two quartiles (Figure 8). As shown in Table 25, the risk classification was improved for all three models with a net gain of cases being reclassified into higher risk categories (NRI index: 13.3% (M_1) – 15.6% (M_2); p-value: 0.003 (M_2) - 0.024 (M_1)), while it did not significantly reduce the classification accuracy for controls. Table 26 shows that the improved reclassification for female cases occurs when individuals classified as lower risk group by models without the 13-SNPs GRS were reclassified into a higher risk group by models with the GRS.

5.3.4.3 156-SNPs GRS

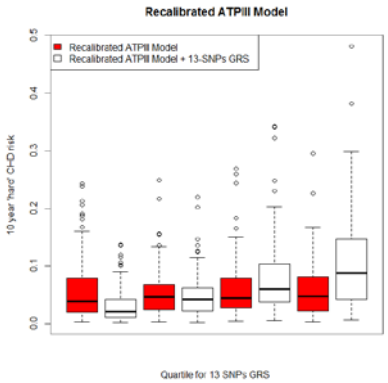
Table 27 shows the performance of the various prediction models before and after including the 156-SNPs GRS in women. The best model was M_2. The 156-SNPs GRS were strongly associated with incident 'hard' CHD in all three models. Women in the highest quartile of the 156-SNPs GRS (>131) had a higher CHD risk, varying from 2.19-fold in M_2 to 2.41-fold in M_1 than those in the lowest quartile (<121).

Table 26: Risk reclassification table (base model with and without 13-SNPs GRS) for female cases of coronary heart disease

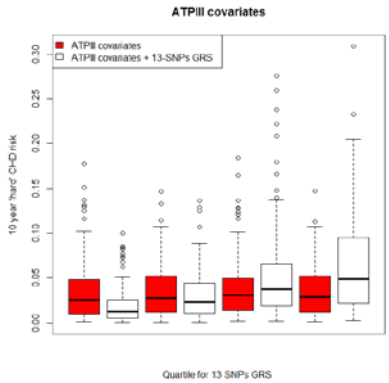
	0-5%	5-10%	10-20%	20% above
M_1: Recalibrated Framingham Risk Model	Recalibrated Framingham Risk Model + 13 SNPs			
0-5%	38	16	0	0
5-10%	12	13	19	0
10-20%	0	8	16	2
20% above	0	0	0	4
M_2: ATPIII covariates	ATPIII covariates + 13 SNPs			
0-5%	67	19	0	0
5-10%	11	11	10	2
10-20%	0	2	4	2
20% above	0	0	0	0
M_3: ATPIII covariates + hsCRP + creatinine	ATPIII covariates + hsCRP + creatinine + 13 SNPs			
0-5%	70	16	0	
5-10%	8	7	8	1
10-20%	0	4	4	6
20% above	0	1	0	3

hsCRP: high-sensitivity C-reactive protein

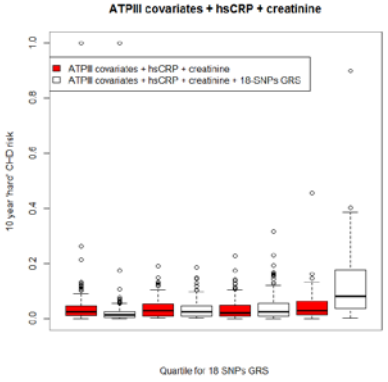
Figure 8: Boxplots of 10-year of coronary heart disease risk estimated using different models with and without 13-SNPs GRS, by quartiles of 13-SNPs GRS in women. (A) Recalibrated Framingham Risk Model (M_1); (B) ATPIII covariates (M_2); (C) ATPIII covariates + hsCRP + creatinine (M_3)



(A)



(B)



(C)

Table 27: Performance of various prediction models of coronary heart disease with and without 156-SNPs Genetic Risk Score for women

Models	Quartiles of $GRS_{[Range]}$	Hazard Ratio (95% CI)	P-value	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)
M_1: Recalibrated Framingham Risk Model				0.765(0.026)	-	-
M_1+ GRS	$Q1_{[104,121]}$	1.000	-	0.794(0.026)	**0.117(0.036)**	0.016(0.609)
	$Q2_{[122,126]}$	0.546(0.288,1.038)	0.065			
	$Q3_{[127,131]}$	1.608(1.002,2.581)	**0.049**			
	$Q4_{[132,144]}$	2.412(1.491,3.902)	**$3.35x10^{-4}$**			
M_2: ATPIII covariates				0.773(0.026)	-	-
M_2+ GRS	$Q1_{[104,121]}$	1.000	-	0.798(0.026)	**0.117(0.011)**	-0.021(0.377)
	$Q2_{[122,126]}$	0.495(0.258,0.949)	**0.034**			
	$Q3_{[127,131]}$	1.507(0.926,2.452)	0.099			
	$Q4_{[132,144]}$	2.194(1.344,3.582)	**0.002**			
M_3: ATPIII covariates + hsCRP + creatinine				0.771(0.026)	-	-
M_3 + GRS	$Q1_{[104,121]}$	1.000	-	0.794(0.026)	**0.148(0.001)**	0.002(0.949)
	$Q2_{[122,126]}$	0.454(0.234,0.880)	**0.019**			
	$Q3_{[127,131]}$	1.584(0.974,2.575)	0.064			
	$Q4_{[132,144]}$	2.304(1.408,3.771)	**$9.01x10^{-4}$**			

Cl: Confidence Interval; NRI: net reclassification improvement; SE: standard error

hsCRP: high-sensitivity C-reactive protein

Improvements in discrimination were evaluated for the inclusion of the GRS to the three models predicting risk of 'hard' CHD in women. In all three models, adding the 156-SNPs GRS into the base models provided great improvement in c-statistics (Table 27). The largest increase also occurred when adding the 156-SNPs GRS to M_1, the recalibrated Framingham risk model, the same as in men. The c-statistic increased from 0.765 to 0.794. The c-statistic of the best performing model, M_2, reached 0.798 after adding the 156-SNPs GRS. The addition of the 156-SNPs GRS to all three models resulted in attaining c-statistics that are very close to 0.80, which is the threshold for excellent discrimination according to the gauge for interpretation set by Hosmer et al [240].

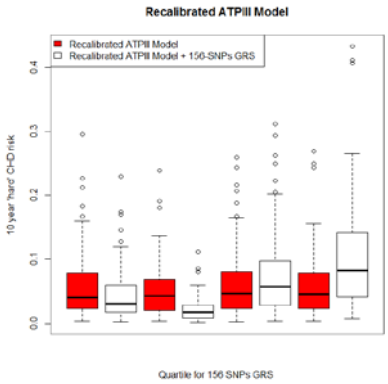
In terms of absolute risk, adding the 156-SNPs GRS into the base models also led to lower absolute risks for individuals in the first two quartiles while higher absolute risks for individuals in the latter two quartiles (Figure 9), which was a similar observation in men. As shown in Table 27, the risk classification was improved for all three models with a net gain of cases being reclassified into higher risk categories (NRI index: 11.7% (M_1 and M_2) - 14.8% (M_3); p-value: 0.001 (M_3) - 0.036 (M_1)), while it did not significantly reduce the classification accuracy for controls. Table 28 shows that the improved reclassification for female cases occurs when individuals classified as lower risk group by models without the 156-SNPs GRS were reclassified into a higher risk group by models with the GRS.

Table 28: Risk reclassification table (base model with and without 156-SNPs GRS) for female cases of coronary heart disease

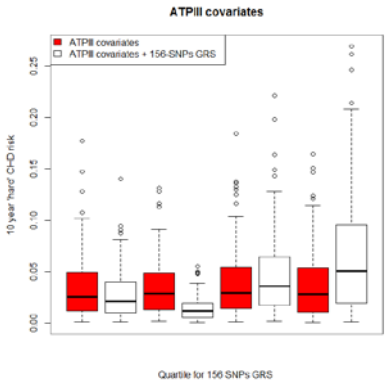
	0-5%	5-10%	10-20%	20% above
M_1: Recalibrated Framingham Risk Model	Recalibrated Framingham Risk Model + 156 SNPs			
0-5%	41	13	0	0
5-10%	11	19	14	0
10-20%	0	6	14	6
20% above	0	0	1	3
M_2: ATPIII covariates	ATPIII covariates + 156 SNPs			
0-5%	72	14	0	0
5-10%	7	20	7	0
10-20%	0	3	1	4
20% above	0	0	0	0
M_3: ATPIII covariates + hsCRP + creatinine	ATPIII covariates + hsCRP + creatinine + 156 SNPs			
0-5%	70	16	0	0
5-10%	5	12	7	0
10-20%	0	3	7	4
20% above	0	0	0	4

hsCRP: high-sensitivity C-reactive protein

Figure 9: Boxplots of 10-year of coronary heart disease risk estimated using different models with and without 156-SNPs GRS, by quartiles of 156-SNPs GRS in women. (A) Recalibrated Framingham Risk Model (M_1); (B) ATPIII covariates (M_2); (C) ATPIII covariates + hsCRP + creatinine (M_3)



(A)



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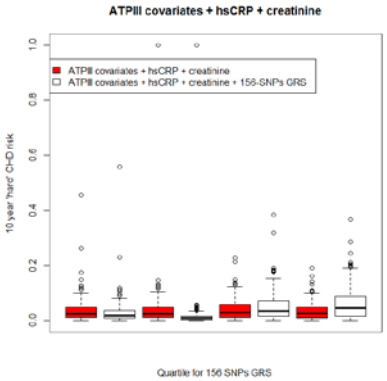


(C)

5.3.4.4 51-SNPs GRS

Table 29 shows the performance of the various prediction models before and after including the 51-SNPs GRS in women. The best model was M_3. The 51-SNPs GRS were strongly associated with incident 'hard' CHD in all three models with different adjustment. Women in the highest quartile of the 51-SNPs GRS (>51) had a higher CHD risk, varying from 11.24-fold in M_1 to 12.37-fold in M_3 than those in the lowest quartile (<46).

Improvements in discrimination were evaluated for the inclusion of the GRS to the three models predicting risk of 'hard' CHD in women. In all three models, adding the 51-SNPs GRS into the base models improved c-statistics to a great extent (Table 28). The largest increase also occurred when adding the 51-SNPs GRS to M_3. The c-statistic increased from 0.771 to 0.828. The c-statistic of the best performing model, M_3, reached 0.828 after adding the 51-SNPs GRS. The addition of the 51-SNPs GRS into all three different models reached 0.80 which indicated the new models provided excellent discrimination according to the gauge for interpretation set by Hosmer et al [240].

In terms of absolute risk, adding the 51-SNPs GRS into the base models also led to lower absolute risks for individuals in the first two quartiles while higher absolute risks for individuals in the latter two quartiles (Figure 10). As shown in Table 29, the risk classification was improved for all three models with a net gain of cases

Table 29: Performance of various prediction models of coronary heart disease with and without 51-SNPs Genetic Risk Score for women

Models	Quartiles of $GRS_{[Range]}$	Hazard Ratio (95% CI)	P-value	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)
M_1: Recalibrated Framingham Risk Model				0.765(0.026)	-	-
M_1+ GRS	$Q1_{[35, 45]}$	1.000	-	**0.821(0.026)**	**0.258(2.43×10^{-6})**	0.003(0.921)
	$Q2_{[46, 48]}$	4.148(2.085,8.253)	**5.06×10^{-5}**			
	$Q3_{[49, 51]}$	3.998(2.030,7.871)	**6.11×10^{-5}**			
	$Q4_{[52, 64]}$	11.236(5.855,21.562)	**3.49×10^{-13}**			
M_2: ATPIII covariates				0.773(0.026)	-	-
M_2 + GRS	$Q1_{[35, 45]}$	1.000	-	**0.825(0.026)**	**0.313(7.76×10^{-9})**	-0.020(0.422)
	$Q2_{[46, 48]}$	4.856(2.404,9.808)	**1.05×10^{-5}**			
	$Q3_{[49, 51]}$	5.089(2.543,10.180)	**4.30×10^{-6}**			
	$Q4_{[52, 64]}$	12.310(6.371,23.800)	**8.13×10^{-14}**			
M_3: ATPIII covariates + hsCRP + creatinine				0.771(0.026)	-	-
M_3 + GRS	$Q1_{[35, 45]}$	1.000	-	**0.828(0.026)**	**0.281(2.03×10^{-7})**	-0.002(0.925)
	$Q2_{[46, 48]}$	4.939(2.439,10.000)	**9.11×10^{-6}**			
	$Q3_{[49, 51]}$	5.128(2.554,10.300)	**4.29×10^{-6}**			
	$Q4_{[52, 64]}$	12.370(6.393,23.930)	**8.08×10^{-14}**			

Cl: Confidence Interval; NRI: net reclassification improvement; SE: standard error

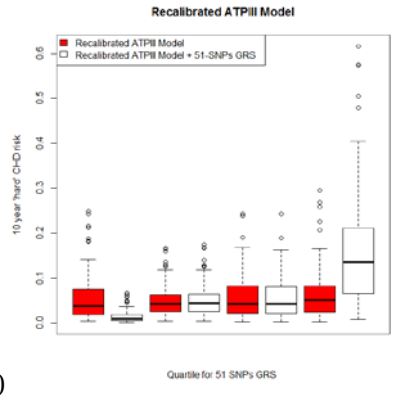
hsCRP: high-sensitivity C-reactive protein

Table 30: Risk reclassification table (base model with and without 51-SNPs GRS) for female cases of coronary heart disease

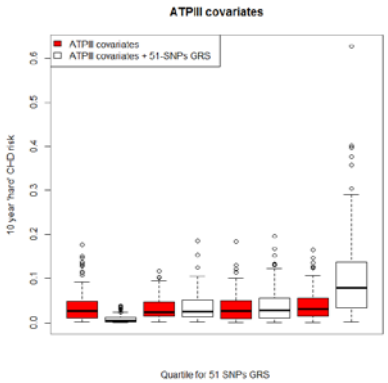
	0-5%	5-10%	10-20%	20% above
M_1: Recalibrated Framingham Risk Model	Recalibrated Framingham Risk Model + 51 SNPs			
0-5%	38	9	7	0
5-10%	5	22	10	7
10-20%	2	0	16	8
20% above	0	1	0	3
M_2: ATPIII covariates	ATPIII covariates + 51 SNPs			
0-5%	62	16	8	0
5-10%	3	14	14	3
10-20%	1	0	4	3
20% above	0	0	0	0
M_3: ATPIII covariates + hsCRP + creatinine	ATPIII covariates + hsCRP + creatinine + 51 SNPs			
0-5%	63	16	7	0
5-10%	1	12	9	2
10-20%	2	2	2	8
20% above	1	0	0	3

hsCRP: high-sensitivity C-reactive protein

Figure 10: Boxplots of 10-year of coronary heart disease risk estimated using different models with and without 51-SNPs GRS, by quartiles of 51-SNPs GRS in women. (A) Recalibrated Framingham Risk Model (M_1); (B) ATPIII covariates (M_2); (C) ATPIII covariates + hsCRP + creatinine (M_3)



(A)



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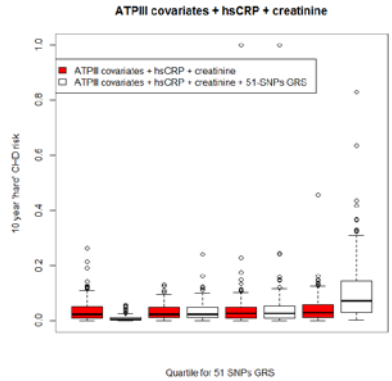


(C)

being reclassified into higher risk categories (NRI index: 25.8% (M_1) – 31.3% (M_2); p-value: 7.76 $x10^{-9}$ (M_2) - 2.43 $x10^{-6}$ (M_1)), while it did not significantly reduce the classification accuracy for controls. Table 30 shows that the improved reclassification for female cases occurs when individuals classified as lower risk group by models without the 51-SNPs GRS were reclassified into a higher risk group by models with the GRS.

5.4 Discussion

The aim of this study was to evaluate whether genetic factors could provide additional information for the prediction of incident 'hard' CHD beyond the use of traditional risk factors and biomarkers. We found that all the GRS were significantly associated with incident 'hard' CHD after adjustment for traditional risk factors and recent ones such as hsCRP and creatinine. In addition to the significant association, the inclusion of the GRS into the phenotypic risk models led to the improvement in discrimination and risk classification in most situations. The significant association and the improvement in discrimination and classification suggested that the GRS was constituted with the appropriate predictive SNPs associated with CHD and its risk factors. It is hence an independent predictor of 'hard' CHD over and above traditional risk factors as shown by comparison with M_2. The GRS remains as an independent predictor even when compared with model M_3 which contains the more recent biomarkers hsCRP and creatinine.

Several previous studies have incorporated genetic factors into the non-genetic based model. Investigators began by adding a single SNP into the model and the SNPs most frequently used were from 9p21.3, a region reported to be highly associated with CHD. However, the results were controversial [167, 241]. We have also tested the predictiveness of the SNPs in this region but found no improvement for both model discrimination and risk classification (Table 31). We also constructed two sets of GRS containing different number of SNPs. One set only included SNPs reported to be associated with CHD or MI in GWAS publications. The other set included SNPs associated with CHD related traits on the basis of the prior set. We found that the performance of the GRS containing larger number of SNPs was better (18-SNPs vs 156-SNPs; 13-SNPs vs 51-SNPs) than the GRS including only a small set of SNPs in terms of their effect sizes, model discrimination and risk classifications in both men and women. One possibility could be due to the modest effect of the single SNP and it has been suggested that hundreds of SNPs with modest effect size would be needed to improve risk prediction [242, 243].

In our study, all the SNPs were retrieved from the GWAS catalog [78] and had been reported to be associated with CHD and its risk factors. We used two different selection criteria to choose SNPs included in the GRS. It is found that the performance of the GRS containing SNPs selected using the second approach (SNPs filtered by the Cox proportional hazards models with adjustments for age and gender) performed much better (13-SNPs vs 18-SNPs; 51-SNPs vs 156-SNPs) than the GRS

Table 31: Performance of various prediction models of coronary heart disease with and without the SNP from 9p21.3

Models	Men			Women		
	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)	C-statistic (SE)	Cases NRI (p-value)	Controls NRI (p-value)
M_1: Recalibrated Framingham Risk Model	0.663(0.021)	-	-	0.765(0.026)	-	-
M_1+ GRS	0.675(0.018)	0.011(0.639)	0.004(0.791)	0.775(0.026)	0.008(0.835)	0.008(0.720)
M_2: ATPIII covariates	0.679(0.018)	-	-	0.773(0.026)	-	-
M_2 + GRS	0.683(0.018)	-0.022(0.317)	-0.011(0.423)	0.778(0.026)	0(1.000)	-0.005(0.689)
M_3: ATPIII covariates + hsCRP + creatinine	0.695(0.018)	-	-	0.771(0.026)	-	-
M_3 + GRS	0.699(0.018)	0.008(0.758)	0.011(0.513)	0.776(0.026)	0.016(0.593)	0.008(0.637)

containing SNPs selected using the first approach (SNPs robustly associated with CHD and its risk factors). Although the extent of improvement of c-statistics was smaller in women than those in men when compared to the same base model and the same GRS, the addition of GRS to all models resulted in better c-statistics in women. After incorporating the 51-SNPs GRS into the three base models in women, c-statistics were all above 0.80, indicating the new model with 51-SNPs GRS could provide excellent discrimination. However, since we selected the SNPs and did the analysis in the same population and with our relatively small sample size, we believe that these models may be over-fitted and may not represent its true predictive performance. Hence, additional Chinese cohorts will be needed to confirm if the 13-SNPs and 51-SNPs GRS could perform consistently well across independent populations.

Some studies have shown that newer biomarkers, such as hsCRP are independent risk predictors in addition to traditional risk factors [54, 244]. It was found previously in the SCHS that hsCRP and creatinine but not HbA1c, could improve risk prediction when combined with conventional risk factors [203]. Hence we were interested in the improvement of prediction accuracy by adding the GRS to a model that included conventional risk factors (M_2), and even one that included hsCRP and creatinine (M_3). We found that the inclusion of GRS could indeed further improve the model discrimination compared to the model that already included traditional risk factors and the two additional biomarkers. The comparisons were made with the

recalibrated ATPIII model as the base model (M_1). Compared with the coefficients generated from the local cohort, those from the FHS were more reliable since they were generated from a much larger cohort and have been demonstrated to be applicable to Asian populations [165]. We found that incorporating the GRS into the recalibrated ATPIII model resulted in improvement in discrimination and classification in both men and women. Indeed, the c-statistic and NRI indices achieved were almost as good as when the GRS score was incorporated into the locally-fitted model. Since recalibrated ATP III model is widely-used in clinical settings, this result suggests the potential of including GRS in clinical use, especially with the increasing number of SNPs being identified to be associated with the disease.

Some limitations of our study are as follow. First, the genotypes of the SNPs included in this analysis were obtained from a previous genome-wide association study for 'hard' CHD in the Singaporean Chinese [209, 245, 246]. We did not carry out any specific genotyping for any SNPs needed in the prediction study. For those SNPs without genotype information, we made use of imputation data which has not been confirmed by genotyping and thus could be less accurate. Second, we only considered the direct effect of genetic factors. It is believed that gene-gene and gene-environment interactions could also play a role in the etiology of the disease. Thus the interaction might also be able to improve prediction accuracy. However, there are no results for interactions that have been robustly confirmed in large scale

analysis thus far. Third, we estimated and tested the GRS effects in the same sample set. Since our sample size is relatively small, we could not afford to split it into a separate training and validation dataset. We realized there can be over-fitting with our results and have tried to minimize this by performing internal cross-validation when reporting the results. However, external replication in independent cohorts is ultimately needed for further validation of the GRS. Forth, in our study, only SNPs from GWAS studies for CHD and its related traits were included and individually they only explain a small proportion of the variance / heritability of these traits. We believe that with additional studies to identify more common variants and other variants not effectively captured by GWAS, such as rare variants and structural variants, and include them in future models may further improve risk prediction accuracy.

In summary, we have shown that the GRS could be an independent predictor for the risk of incident 'hard' CHD in addition to the conventional risk factors and biomarkers. All the GRS were found to be significantly associated with 'hard' CHD and improved for model discrimination and risk classification when added to phenotype based models. Our results suggest the potential of applying genetic factors in the clinical setting. Additional research should be done to further confirm the effect of the GRS for identifying individuals most at risk for early intervention and treatment.

Chapter 6: Interactions between genes and dietary intake and their effect on body mass index in the Singaporean Chinese population

6.1 Introduction

Overweight and obesity, which are defined as the excessive accumulation of fat, are major health problems all over the world. According to the report from the World Health Organization updated in 2015, worldwide obesity has been more than two times higher since 1980. More than 1.9 billion (39%) adults aged 18 years old and above were overweight, and over 600 million (13%) were obese in 2014 [31]. Individuals who are overweight or obese have significantly higher mortality and morbidity rate than those with normal weight due to various health disorders such as type 2 diabetes, cardiovascular diseases, hypertension, musculoskeletal disorders, respiratory complications and certain types of cancer [247-249]. The substantial increase of overweight and obesity prevalence in recent decades is mainly due to widespread adoption of westernized lifestyles, which is characterized by increased energy intake (excessive diet intake) and decreased energy expenditure (lack of physical activity and sedentary lifestyle) [247]. It presents enormous health and finance burdens on individuals, societies and health care systems worldwide, including Asia [250].

Obesity is a complex disease, which is associated with both environmental factors, such as dietary intake and physical inactivity and genetic factors [31-33]. With the

rapid development of GWAS, it is possible to assess many SNPs across the genome and uncover SNPs that are associated with obesity. Recent GWAS has identified 97 independent loci that were associated with BMI, a commonly used measurement to access overweight and obesity. The BMI variation accounted by these 97 loci was estimated to be around 2.7% and it is suggested that the variation explained by genome-wide common variants could be more than 20% [251]. However, previous observations reported that BMI has an estimated heritability around 40%–70% [32, 252]. The 'missing' heritability of BMI might be partially explained by gene-environment interaction studies.

Previous studies were mostly focused on investigating whether the association between BMI and genetic components could be affected by physical activity, smoking or a certain type of dietary factors [253-258]. In addition, these studies usually only chose SNPs from regions that were reported to be strongly associated with BMI or obesity, such as *FTO* and melanocortin 4 receptor (*MC4R*) and were conducted in European-ancestry populations [36-39]. Limited study systematically investigates whether dietary intake could modify BMI associations at known GWAS BMI risk loci, especially in East-Asians.

The study was conducted in 3,758 subjects from two independent Singaporean Chinese cohorts, the SCHS and the SP2. The aims of this study were to investigate: (1) the association between dietary variables and BMI; (2) the association between

these dietary components and genetic factors; (3) whether the association between BMI and BMI risk loci could be modified by dietary intake.

6.2 Methods

6.2.1 Study population

We studied 3,758 participants from two independent adult Singaporean Chinese cohorts (SCHS: N = 1,664; SP2: N = 2,094). All study subjects gave written informed consent. Detailed information regarding these two cohorts was described previously in chapter 3.

6.2.2 Body composition and dietary data

In SCHS, weight and height were self-reported via in-person interviews [259, 260] and were shown to be highly valid across populations [261] including Asians [262]. Since BMI was used as outcome in our study, we excluded those without information for both height and weight to improve the accuracy of the analysis. In SP2, a wall mounted measuring tape and a digital scale were used to measure height and weight respectively [263]. BMI was calculated as weight in kilograms (kg) divided by height in meter square (m^2).

In SCHS, information on dietary components was collected by using a semi-quantitative food-frequency questionnaire (FFQ) specifically developed for this population during the baseline interview. A total of 165 food items commonly

consumed in the Singapore Chinese were assessed by the questionnaire, and the study participants provided the usual frequency and portion size on each of the food and beverage items referring to accompanying photographs to select from 8 food-frequency categories (ranging from never or hardly ever to two or more times/d) and 3 portion sizes. The FFQ was subsequently validated against a series of 24-hour dietary recall interviews [188]. The corrected correlation coefficients for selected energy or nutrients ranged from 0.24 to 0.79 [188, 264].

In SP2, a semi-quantitative FFQ, which contains 169 validated food items and used in the National Nutrition Surveys was utilized to collect dietary intake information during the month prior to the interview [263, 265]. The estimation of the frequency for consuming each food, based on a standard portion size specific for that food group was requested from the participants. The consumption frequency could be reported as per day, per week, per month, rarely or never. Nutrient intakes were computed by the Health Promotion Board of Singapore by use of their in-house database.

Ten dietary variables examined in this study were total calories (kcal/day), cholesterol (mg/day), starch (g/day), dietary fiber (g/day), percentage of energy from protein (%protein), percentage of energy from fat (%fat), percentage of energy from SFA (%SFA), percentage of energy from MFA (%MFA), percentage of energy from PFA (%PFA) and percentage of energy from carbohydrate (%carbohydrate).

6.2.3 SNP selection and genotyping

Large scale GWAS study has identified 97 independent BMI-associated loci in European ancestry population [251]. Among them, 64 SNPs were either genotyped or imputed both in SCHS and SP2. The procedure of genotyping and quality control were described in detail previously in chapter 3.

6.2.4 Statistical analysis

A weighted genetic risk score (wGRS) was calculated based on the 64 BMI-associated variants, where the number of BMI increasing alleles were weighted by their reported effect estimates from recent large-scale GWAS studies [251]. We converted macronutrients (protein, fat, saturated fatty acid (SFA), monounsaturated fatty acid (MFA), polyunsaturated fatty acid (PFA) and carbohydrate) to nutrient density expressed as percent calories or weight per 1,000 kcal and the micronutrients (cholesterol, starch and fiber) to calorie-adjusted nutrient value based on the method of residuals [266]. BMI and all the dietary factors were Z-score transformed as they were not normally distributed. Continuous variables were presented as mean ± SD while categorical variables were displayed as N (%). Differences between means of continuous variables were evaluated by Kruskal-Wallis rank test and differences in frequencies of categorical variables were evaluated by Pearson's χ^2 test. Linear regression analyses between Z-BMI and dietary factors were performed and adjusted for age, sex and calorie intake. Association between the 64 SNPs and BMI/dietary components were evaluated by linear regression with adjustment for age and gender.

Interaction analyses were performed by introducing the interaction term (dietary factor x SNP) with the specific dietary factor and SNP included as covariates in the same regression model. Analysis was carried out in each cohort individually and subsequently meta-analyzed using the inverse-variance weighted method. Since it is not advisable to study gene-environment interactions in subjects with disease [255], we conducted meta-analysis both in SCHS + SP2 (4 datasets: SCHS cases, SCHS controls, SP2610 and SP21m) and SCHS controls + SP2 (3 datasets: SCHS controls, SP2610 and SP21m). Cochran's Q test was used to measure between-study heterogeneity ($P < 0.1$) [267]. All analyses were performed using STATA (version 12.1, Statacorp, College Station, TX, USA). Adjusted P value of <0.05 (2 tailed) was considered statistically significant after adjusting for multiple comparison. The power to detect the associations was estimated by QUANTO (Version 1.2.4) according to different effect size of genotype, dietary factors and interaction (Table 32).

6.3 Result

The study was conducted to investigate the association between dietary components and BMI. In addition, we were also interested in whether intake of various dietary components modifies the association between known index variants at obesity risk loci and BMI in Singaporean Chinese population.

Table 32: Power Estimation of gene-diet interaction for BMI

Minor allele frequency	Modifying factor	Beta for genotype	Beta for Diet	Beta for interaction	Power (%)
0.10	Diet (Population Prevalence of 25%)	0.10	0.20	0.80	72.01%
				1.00	88.90%
				1.20	96.86%
		0.10	0.40	0.80	72.13%
				1.00	88.99%
				1.20	96.90%
		0.10	0.80	0.80	72.52%
				1.00	89.28%
				1.20	97.04%
		0.20	0.20	0.80	72.05%
				1.00	88.93%
				1.20	96.88%
		0.20	0.40	0.80	72.17%
				1.00	89.02%
				1.20	96.92%
		0.20	0.80	0.80	72.56%
				1.00	89.31%
				1.20	97.05%

6.3.1 Demographic and clinical characteristics of study populations

The main demographic and clinical characteristics of the study subjects are presented in Table 33. In total, 3,758 individuals (1,664 from SCHS, 2,094 from SP2) had data available for analysis. As can be seen, BMI level was significantly higher in SCHS, especially in CHD cases (P<0.001). Subjects in SCHS had significant lower intake of total calories (P<0.001), %fat (P<0.001), %SFA (P<0.001), %MFA (P<0.001), %PFA (P<0.001), cholesterol (P<0.001) and fiber (P<0.001) but significantly higher intake of %carbohydrate (P<0.001) than those in SP2. Levels of %protein (P=0.130) and starch (P=0.069) intake were similar in these two cohorts. Individuals in SCHS were much older than those from SP2 (P<0.001) and the percentage of male was significantly lower in SP2 (P<0.001), especially in SP2610. Thus age and gender were included in the model as covariates in subsequent analysis. The weighted GRS was similar across study cohorts (P=0.650).

Table 33: Clinical characteristics of the study participants

	SCHS cases	SCHS controls	SP2610	SP21m
BMI (kg/m2)	23.25 ± 3.48	22.83 ± 3.27	22.62 ± 3.88	22.89 ± 3.47
Age (years)	66.14 ± 7.83	65.98 ± 7.78	48.48 ± 11.42	46.76 ± 10.36
Gender (male %)	389 (65.49%)	699 (65.33%)	268 (23.41%)	605 (63.75%)
Calories (kcal/day)	1642.12 ± 600.70	1638.09 ± 561.71	1853.89 ± 761.45	2115.58 ± 839.03
%Protein1	15.02 ± 2.51	15.09 ± 2.50	15.08 ± 2.02	14.80 ± 1.95
%Fat[1]	24.86 ± 5.80	24.90 ± 5.56	28.30 ±5.70	28.63 ± 5.63
%SFA[1]	8.75 ± 2.50	8.73 ± 2.55	10.58 ± 2.62	10.77 ± 2.67
%MFA[1]	8.49 ± 2.13	8.41 ± 2.07	9.87 ± 2.63	10.01 ± 2.57
%PFA[1]	4.98 ± 1.82	5.13 ± 1.85	6.04 ±2.52	5.97 ± 2.44
Cholesterol (mg/day)	184.69 ± 114.18	184.35 ± 116.00	225.94 ± 139.26	260.61 ± 150.56
%Carbohydrate[1]	59.38 ± 7.57	59.14 ± 7.23	56.40 ± 6.57	56.17 ± 6.59
Starch (g/day)	174.54 ± 71.07	170.89 ± 66.31	163.67 ± 70.18	189.93 ± 78.11
Fiber (g/day)	12.86 ± 5.43	13.19 ± 5.75	19.77 ± 8.50	21.92 ± 9.29
wGRS	58.65 ± 4.72	58.73 ± 4.92	58.48 ± 4.76	58.49 ± 4.76

Data was presented as Mean ± SD or N (%). [1] Represented as a % of Total Energy.
wGRS: weighted Genetic Risk Score; PUFA: Polyunsaturated Fatty Acids; SFA: Saturated Fatty Acids; MUFA: Monounsaturated Fatty Acids

6.3.2 Main effect of SNP on BMI

We first tested the association between BMI susceptibility loci and Z-BMI. Among the 64 overlapping SNPs, 54 of them showed directionally consistent association with BMI as reported previously [251] of which 5 loci (*GNPDA2, KCNK3, NT5C2, QPCTL* and *MC4R)* were significantly associated with the outcome ($P < 0.05$, Table 34). Differing from previous studies conducted in European and Pakistan populations [251, 255], in our meta-analysis, the locus that was most strongly associated with BMI in our Singaporean Chinese populations was rs10938397 on *GNPDA2* ($\beta=0.078$, SE=0.026, P=0.002). While for *MC4R* rs6567160, the strongest associated locus in European and Pakistan only showed nominal significant association with BMI ($\beta=0.062$, SE=0.031, P=0.043) in our population.

6.3.3 Main effect of dietary components on BMI

The association between dietary components and Z-BMI was also evaluated by linear regression. Total calories (P=0.004), starch (P=0.006), %protein (P=0.019), %fat (P=0.009), %MFA (P=0.009) showed statistically significant positive associations with BMI ($P<0.05$). Cholesterol (P=0.011) and %carbohydrate (P=0.034) were significantly associated with BMI negatively (Figure 11). Fiber, %SFA and %PFA were not associated with the outcome (Table 35).

After adjusting for multiple comparison, only total calories intake was significantly associated with Z-BMI ($\beta=0.049$, SE=0.017, $P_{adjust}=0.040$), which showed that a 0.049 change in Z-BMI for every 1 SD change in total calories.

Table 34: Association between 64 SNPs and BMI

	SNPs	Chr	Position	TA	TAF	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m				SCHS control + SP2610 + SP21m			
						Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Q_{pvalue}	Beta	SE	P	Q_{pvalue}
1	rs1000940	17	5223976	G	0.634	-0.021	0.059	0.728	0.091	0.045	0.042	-0.036	0.041	0.383	0.022	0.047	0.643	0.015	0.023	0.508	0.186	0.022	0.025	0.385	0.112
2	rs1016287	2	59159129	T	0.247	0.012	0.064	0.853	4.84E-04	0.049	0.992	-0.003	0.049	0.947	-0.048	0.050	0.345	-0.012	0.026	0.657	0.865	-0.016	0.029	0.569	0.750
3	rs10182181	2	25003800	G	0.427	0.057	0.058	0.326	0.043	0.044	0.327	0.018	0.042	0.671	-0.055	0.045	0.217	0.012	0.023	0.615	0.336	0.003	0.025	0.902	0.265
4	rs10733682	9	128500735	A	0.761	0.023	0.065	0.731	0.017	0.052	0.736	0.005	0.047	0.919	0.093	0.055	0.095	0.032	0.027	0.236	0.651	0.034	0.029	0.253	0.447
5	rs10938397	4	44877284	G	0.271	0.081	0.065	0.209	0.091	0.048	0.059	0.001	0.047	0.988	0.155	0.051	0.003	0.078	0.026	**0.002**	0.165	0.078	0.028	**0.006**	**0.078**
6	rs10968576	9	28404339	G	0.171	0.044	0.077	0.570	0.015	0.058	0.798	-0.063	0.054	0.237	0.047	0.060	0.439	0.002	0.030	0.937	0.497	-0.005	0.033	0.875	0.360
7	rs11030104	11	27641093	A	0.504	0.034	0.056	0.548	0.033	0.042	0.438	0.090	0.040	0.025	0.002	0.044	0.973	0.043	0.022	0.056	0.503	0.044	0.024	0.069	0.314
8	rs11126666	2	26782315	A	0.703	0.126	0.061	0.040	0.040	0.047	0.389	0.011	0.046	0.810	0.093	0.049	0.059	0.059	0.025	**0.017**	0.396	0.046	0.027	0.091	0.466
9	rs11191560	10	104859028	C	0.275	-0.029	0.066	0.663	0.149	0.049	0.002	0.070	0.045	0.121	-0.026	0.053	0.620	0.054	0.026	**0.038**	**0.051**	0.069	0.028	**0.015**	**0.052**
10	rs11583200	1	50332407	C	0.920	0.014	0.094	0.885	0.187	0.079	0.017	0.003	0.076	0.964	0.014	0.088	0.870	0.060	0.042	0.152	0.297	0.071	0.047	0.127	0.184
11	rs11688816	2	62906552	G	0.704	0.049	0.063	0.438	0.039	0.048	0.423	-0.057	0.045	0.200	0.013	0.050	0.795	0.003	0.025	0.891	0.402	-0.005	0.027	0.851	0.314
12	rs12286929	11	114527614	G	0.271	-0.042	0.068	0.542	-0.024	0.048	0.620	0.092	0.047	0.049	0.092	0.050	0.067	0.039	0.026	0.126	0.137	0.053	0.028	0.057	0.144
13	rs12429545	13	53000207	A	0.243	0.128	0.068	0.060	-0.046	0.048	0.336	0.078	0.048	0.103	0.055	0.055	0.313	0.042	0.026	0.110	0.133	0.027	0.029	0.350	0.155
14	rs12566985	1	74774781	G	0.820	0.016	0.074	0.825	-0.003	0.056	0.952	0.127	0.053	0.018	0.011	0.060	0.857	0.044	0.030	0.141	0.313	0.049	0.033	0.130	0.183
15	rs12940622	17	76230166	G	0.697	0.096	0.062	0.120	-0.005	0.047	0.924	0.043	0.044	0.333	0.009	0.048	0.858	0.030	0.025	0.229	0.581	0.017	0.027	0.526	0.750
16	rs13021737	2	622348	G	0.928	0.036	0.113	0.748	0.115	0.082	0.162	0.093	0.076	0.221	0.028	0.090	0.753	0.076	0.044	0.084	0.879	0.083	0.048	0.082	0.766
17	rs13201877	6	137717234	G	0.038	0.055	0.182	0.764	0.111	0.108	0.303	0.121	0.105	0.253	-0.019	0.117	0.871	0.074	0.060	0.215	0.813	0.077	0.063	0.227	0.625
18	rs1441264	13	78478920	A	0.604	0.114	0.060	0.056	0.035	0.044	0.429	-0.029	0.041	0.483	-0.048	0.046	0.299	0.005	0.023	0.812	0.121	-0.014	0.025	0.583	0.388
19	rs1460676	2	164275935	C	0.372	-0.009	0.060	0.884	-0.030	0.045	0.510	0.080	0.041	0.055	0.094	0.046	0.043	0.040	0.023	0.085	0.151	0.049	0.026	0.053	0.105
20	rs1516725	3	187306698	C	0.922	-0.110	0.105	0.296	0.139	0.085	0.102	0.138	0.073	0.058	-0.042	0.085	0.623	0.053	0.042	0.209	0.110	0.085	0.046	0.067	0.207
21	rs1528435	2	181259207	T	0.664	0.056	0.062	0.369	0.032	0.045	0.479	-0.031	0.044	0.485	0.045	0.048	0.352	0.020	0.024	0.415	0.572	0.013	0.026	0.614	0.449
22	rs1558902	16	52361075	A	0.126	-0.172	0.082	0.036	0.024	0.064	0.713	0.044	0.064	0.489	0.139	0.072	0.056	0.021	0.035	0.547	**0.040**	0.064	0.038	0.099	0.460
23	rs16851483	3	142758126	T	0.242	-0.006	0.064	0.932	0.019	0.050	0.701	-0.016	0.046	0.726	0.099	0.053	0.060	0.024	0.026	0.364	0.390	0.029	0.029	0.303	0.251

Table 34 (continued): Association between 64 SNPs and BMI

	SNPs	Chr	Position	TA	TAF	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m				SCHS control + SP2610 + SP21m			
						Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Q_{pvalue}	Beta	SE	P	Q_{pvalue}
24	rs16951275	15	65864222	T	0.407	0.085	0.060	0.157	0.038	0.042	0.368	0.022	0.042	0.603	0.029	0.046	0.531	0.038	0.023	0.102	0.849	0.029	0.025	0.237	0.963
25	rs17203016	2	207963763	G	0.140	0.102	0.087	0.239	0.135	0.063	0.031	0.084	0.057	0.142	-0.057	0.064	0.377	0.064	0.033	0.050	0.163	0.058	0.035	0.101	**0.086**
26	rs17405819	8	76969139	T	0.536	-0.134	0.059	0.024	-0.061	0.043	0.158	0.017	0.041	0.676	0.104	0.045	0.022	-0.005	0.023	0.814	**0.006**	0.018	0.025	0.481	**0.031**
27	rs17724992	19	18315825	A	0.528	0.101	0.057	0.076	0.041	0.044	0.349	-0.015	0.040	0.707	0.023	0.045	0.617	0.028	0.023	0.216	0.407	0.014	0.025	0.568	0.624
28	rs1928295	9	119418304	T	0.607	0.007	0.058	0.900	0.043	0.044	0.336	-0.021	0.040	0.598	0.051	0.046	0.265	0.018	0.023	0.422	0.611	0.021	0.025	0.412	0.412
29	rs2033529	6	40456631	G	0.167	0.111	0.084	0.189	-0.079	0.060	0.188	0.025	0.052	0.632	0.084	0.060	0.159	0.025	0.031	0.421	0.170	0.012	0.033	0.726	0.148
30	rs2033732	8	85242264	C	0.601	0.021	0.057	0.708	0.036	0.045	0.430	0.026	0.042	0.538	-0.019	0.045	0.671	0.016	0.023	0.494	0.836	0.015	0.025	0.561	0.655
31	rs205262	6	34671142	G	0.135	0.065	0.077	0.397	-0.024	0.062	0.696	0.018	0.061	0.769	0.024	0.066	0.713	0.016	0.033	0.620	0.838	0.005	0.036	0.882	0.838
32	rs2075650	19	50087459	A	0.919	-0.059	0.106	0.576	0.232	0.079	0.003	-0.069	0.072	0.334	-0.039	0.081	0.633	0.021	0.041	0.604	**0.020**	0.035	0.044	0.427	**0.010**
33	rs2080454	16	47620091	C	0.489	-0.051	0.060	0.394	-0.016	0.044	0.714	0.059	0.041	0.147	-0.054	0.045	0.234	-0.007	0.023	0.761	0.232	0.001	0.025	0.980	0.161
34	rs2112347	5	75050998	T	0.440	0.003	0.057	0.964	0.010	0.044	0.822	0.109	0.041	0.008	-0.009	0.045	0.847	0.035	0.023	0.126	0.183	0.041	0.025	0.099	0.107
35	rs2176040	2	226801046	A	0.071	-0.112	0.110	0.310	-0.042	0.085	0.622	-0.070	0.080	0.381	0.019	0.086	0.822	-0.046	0.044	0.302	0.794	-0.033	0.048	0.495	0.742
36	rs2207139	6	50953449	G	0.132	-0.032	0.078	0.679	0.070	0.063	0.266	-0.077	0.063	0.222	0.122	0.066	0.066	0.023	0.033	0.485	0.121	0.036	0.037	0.332	**0.075**
37	rs2287019	19	50894012	C	0.812	0.029	0.072	0.686	0.102	0.054	0.062	0.076	0.051	0.138	0.082	0.060	0.174	0.077	0.029	**0.008**	0.883	0.086	0.032	**0.006**	0.937
38	rs2365389	3	61211502	C	0.129	0.029	0.082	0.722	-0.077	0.063	0.222	0.143	0.064	0.026	0.016	0.067	0.805	0.027	0.034	0.434	0.111	0.026	0.037	0.485	**0.050**
39	rs2820292	1	200050910	C	0.200	0.082	0.069	0.236	-0.092	0.057	0.105	0.012	0.051	0.819	0.075	0.056	0.178	0.014	0.029	0.622	0.129	3.70E-05	0.031	0.999	0.105
40	rs2836754	21	39213610	C	0.376	-0.070	0.059	0.241	-0.047	0.045	0.290	-0.007	0.042	0.874	0.028	0.047	0.553	-0.019	0.023	0.414	0.530	-0.010	0.026	0.700	0.509
41	rs29941	19	39001372	G	0.209	0.008	0.073	0.908	0.006	0.052	0.909	-0.009	0.051	0.860	0.052	0.056	0.354	0.013	0.028	0.634	0.875	0.014	0.031	0.639	0.710
42	rs3101336	1	72523773	C	0.919	-0.084	0.109	0.444	0.070	0.080	0.382	0.096	0.072	0.184	0.077	0.086	0.374	0.058	0.042	0.170	0.565	0.082	0.046	0.071	0.967
43	rs3817334	11	47607569	T	0.286	0.001	0.063	0.992	0.091	0.047	0.053	-0.002	0.046	0.957	0.012	0.050	0.806	0.029	0.025	0.258	0.470	0.034	0.028	0.218	0.318
44	rs3849570	3	81874802	A	0.505	0.059	0.057	0.298	0.023	0.044	0.591	0.032	0.040	0.432	-0.015	0.046	0.742	0.022	0.023	0.329	0.766	0.015	0.025	0.541	0.726
45	rs3888190	16	28796987	A	0.086	0.018	0.100	0.860	-0.194	0.077	0.012	0.091	0.072	0.205	-0.013	0.081	0.874	-0.024	0.040	0.544	**0.055**	-0.033	0.044	0.459	**0.025**
46	rs4256980	11	8630515	C	0.594	0.034	0.061	0.571	-0.003	0.044	0.939	0.014	0.041	0.737	-0.093	0.046	0.041	-0.016	0.023	0.500	0.243	-0.024	0.025	0.334	0.185

Table 34 (continued): Association between 64 SNPs and BMI

	SNPs	Chr	Position	TA	TAF	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m				SCHS control + SP2610 + SP21m			
						Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Q_{pvalue}	Beta	SE	P	Q_{pvalue}
47	rs4740619	9	15624326	T	0.239	0.161	0.065	0.013	-0.054	0.051	0.294	-0.028	0.046	0.548	0.044	0.054	0.419	0.014	0.026	0.605	**0.045**	-0.016	0.029	0.586	0.402
48	rs4787491	16	29922838	G	0.447	0.028	0.058	0.635	0.056	0.042	0.183	-0.027	0.041	0.512	-0.030	0.046	0.507	0.005	0.023	0.835	0.419	0.001	0.025	0.980	0.267
49	rs492400	2	219057996	C	0.215	0.075	0.073	0.303	-0.032	0.052	0.543	0.066	0.049	0.181	0.055	0.054	0.310	0.037	0.028	0.179	0.484	0.031	0.030	0.303	0.344
50	rs6567160	18	55980115	C	0.164	0.161	0.079	0.041	0.079	0.056	0.163	0.042	0.055	0.441	0.005	0.062	0.937	0.062	0.031	**0.043**	0.450	0.044	0.033	0.183	0.679
51	rs6804842	3	25081441	G	0.660	0.043	0.060	0.476	0.051	0.046	0.266	0.035	0.044	0.431	-0.040	0.047	0.389	0.020	0.024	0.396	0.496	0.016	0.026	0.538	0.329
52	rs7138803	12	48533735	A	0.256	0.124	0.067	0.065	0.055	0.049	0.270	-0.019	0.046	0.679	-0.094	0.053	0.076	0.005	0.026	0.854	**0.048**	-0.017	0.028	0.561	0.122
53	rs7141420	14	78969207	T	0.479	0.094	0.057	0.101	-0.053	0.043	0.224	-0.023	0.041	0.580	-0.015	0.044	0.741	-0.010	0.023	0.645	0.224	-0.030	0.025	0.225	0.809
54	rs7164727	15	70881044	T	0.252	0.070	0.067	0.295	-0.039	0.049	0.431	0.040	0.047	0.402	0.091	0.051	0.073	0.036	0.026	0.169	0.289	0.030	0.028	0.294	0.178
55	rs7239883	18	38401669	G	0.305	0.097	0.062	0.117	0.002	0.046	0.969	0.009	0.043	0.844	-0.034	0.049	0.489	0.010	0.024	0.687	0.421	-0.006	0.027	0.815	0.793
56	rs7243357	18	55034299	T	0.794	0.053	0.070	0.443	0.029	0.052	0.579	0.083	0.054	0.128	-0.063	0.055	0.253	0.023	0.028	0.409	0.279	0.017	0.031	0.575	0.163
57	rs7599312	2	213121476	G	0.978	-0.227	0.219	0.299	0.396	0.160	0.014	0.034	0.125	0.789	-0.119	0.161	0.459	0.051	0.078	0.520	**0.060**	0.092	0.084	0.276	**0.062**
58	rs7715256	5	153518086	G	0.965	-0.031	0.151	0.840	0.100	0.117	0.392	-0.098	0.115	0.394	-0.040	0.117	0.732	-0.017	0.061	0.788	0.672	-0.014	0.067	0.838	0.464
59	rs7903146	10	114748339	C	0.978	-0.031	0.198	0.874	0.116	0.136	0.394	-0.034	0.146	0.816	0.028	0.153	0.858	0.030	0.077	0.697	0.876	0.041	0.083	0.625	0.750
60	rs9374842	6	120227364	T	0.913	0.093	0.107	0.384	0.071	0.074	0.339	0.038	0.072	0.596	0.067	0.080	0.403	0.063	0.040	0.118	0.976	0.058	0.043	0.182	0.943
61	rs9400239	6	109084356	C	0.705	-0.038	0.064	0.556	0.039	0.047	0.410	0.032	0.045	0.467	0.045	0.051	0.380	0.026	0.025	0.294	0.747	0.038	0.027	0.163	0.982
62	rs9641123	7	93035668	C	0.313	0.011	0.063	0.856	0.067	0.046	0.149	-0.047	0.043	0.277	0.075	0.048	0.118	0.025	0.024	0.310	0.194	0.027	0.026	0.305	**0.097**
63	rs977747	1	47457264	T	0.959	-0.108	0.158	0.494	-0.081	0.111	0.468	0.127	0.109	0.242	-0.045	0.103	0.663	-0.014	0.058	0.803	0.476	5.57E-05	0.062	0.999	0.352
64	rs9914578	17	1951886	G	0.210	-0.022	0.071	0.760	-0.040	0.053	0.447	0.039	0.051	0.453	0.017	0.058	0.764	0.001	0.028	0.977	0.723	0.005	0.031	0.868	0.548

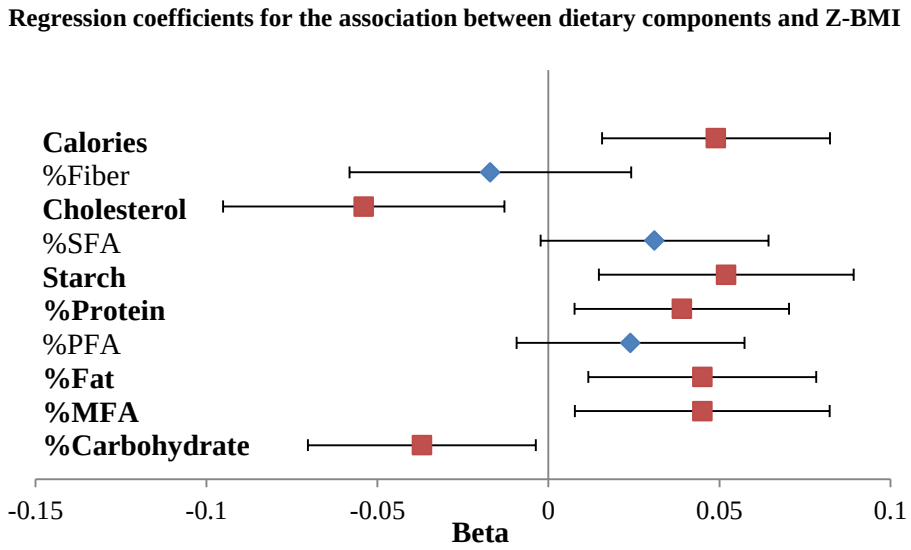
Chr: chromosome; TA: test allele; TAF: test allele frequency; Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant Z-score BMI associations (P < 0 .05) and heterogeneity (Q_{pvalue} < 0.1) findings are in bold.

Table 35: Association between dietary components and BMI

	SCHS cases			SCHS controls			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	$Q_{p\text{-value}}$	Beta	SE	P	P_{adjust}	$Q_{p\text{-value}}$
Calories	0.142	0.045	0.002	0.083	0.033	0.012	-0.002	0.030	0.952	0.026	0.033	0.437	0.049	0.017	0.004	**0.040**	**0.034**	0.033	0.019	0.071	0.710	0.161
Cholesterol	-0.037	0.056	0.514	0.006	0.043	0.890	-0.095	0.037	0.010	-0.064	0.037	0.099	-0.054	0.021	0.011	0.110	0.346	-0.057	0.023	0.013	0.130	0.201
Starch	-0.010	0.047	0.824	0.100	0.037	0.007	0.013	0.034	0.690	0.090	0.038	0.017	0.052	0.019	0.006	0.060	0.123	0.064	0.021	0.002	**0.020**	0.159
Fiber	-0.060	0.056	0.280	-0.018	0.043	0.671	0.027	0.035	0.441	-0.049	0.038	0.206	-0.017	0.021	0.407	1.000	0.414	-0.010	0.022	0.644	1.000	0.338
%Protein[1]	0.049	0.041	0.234	0.031	0.031	0.325	0.033	0.029	0.264	0.048	0.033	0.147	0.039	0.016	0.019	0.190	0.971	0.037	0.018	0.041	0.410	0.921
%Fat[1]	-0.008	0.042	0.848	0.084	0.032	0.008	0.009	0.033	0.773	0.080	0.036	0.028	0.045	0.017	0.009	0.090	0.155	0.057	0.019	0.003	**0.030**	0.198
%SFA[1]	-0.001	0.041	0.985	0.075	0.031	0.017	-0.004	0.032	0.904	0.042	0.037	0.248	0.031	0.017	0.072	0.720	0.280	0.038	0.019	0.046	0.460	0.212
%MFA[1]	0.002	0.042	0.967	0.044	0.032	0.162	0.035	0.031	0.258	0.086	0.035	0.013	0.045	0.019	0.009	0.090	0.454	0.053	0.019	0.004	**0.040**	0.509
%PFA[1]	-0.049	0.041	0.232	0.054	0.031	0.080	-0.011	0.030	0.721	0.079	0.033	0.017	0.024	0.017	0.147	1.000	**0.041**	0.038	0.019	0.035	0.350	0.107
%Carbohydrate[1]	0.005	0.042	0.904	-0.065	0.032	0.039	-0.010	0.032	0.762	-0.063	0.035	0.071	-0.037	0.017	0.034	0.340	0.374	-0.045	0.019	0.017	0.170	0.381

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0.05$) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

Figure 11: Regression coefficients for the associations between dietary components and Z-BMI adjusted for total calories, age, and sex. Components with the red square markers have significant associations with Z-BMI (P <0.05)



6.3.4 Main effect of weighted GRS on various dietary components

The wGRS was significantly associated with Z-BMI in all dataset. After meta-analysis, each unit increase in the wGRS was positively associated with the outcome as shown in Table 36 (β=0.023, SE=0.003, P<0.001).

We also tested the association between wGRS and various dietary components. No significant association was observed as shown in Figure 12 and Table 36.

6.3.5 Interaction between weighted GRS and dietary intake for BMI

After checking the main effect of genetic factors/dietary components on BMI, we tested the interaction between wGRS and various dietary factors on BMI.

Table 36: Association between weighted GRS and dietary factors or BMI

	SCHS cases			SCHS controls			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	$Q_{p\text{-}value}$	Beta	SE	P	P_{adjust}	$Q_{p\text{-}value}$
BMI	0.025	0.008	**0.003**	0.025	0.006	**7.05E-05**	0.022	0.006	**3.35E-04**	0.023	0.007	**0.001**	0.023	0.003	**2.51E-12**	-	0.984	0.023	0.004	**2.00E-10**	-	0.944
Calories	0.006	0.008	0.414	-0.010	0.006	0.087	0.003	0.006	0.580	-0.003	0.007	0.622	-0.002	0.003	0.577	1.000	0.280	-0.003	0.004	0.328	1.000	0.283
Cholesterol	-0.014	0.009	0.102	0.004	0.006	0.551	0.009	0.006	0.118	-0.004	0.007	0.548	0.001	0.003	0.801	1.000	0.123	0.004	0.004	0.334	1.000	0.328
Starch	0.002	0.009	0.777	-0.001	0.006	0.893	-0.005	0.006	0.442	0.003	0.007	0.651	-0.001	0.003	0.871	1.000	0.833	-0.001	0.004	0.767	1.000	0.696
Fiber	0.002	0.009	0.805	-0.002	0.006	0.794	-0.006	0.006	0.277	0.004	0.007	0.530	-0.001	0.003	0.736	1.000	0.660	-0.002	0.004	0.640	1.000	0.490
%Protein[1]	-0.011	0.009	0.219	-0.001	0.006	0.927	0.005	0.006	0.432	0.002	0.007	0.744	2.08E-04	0.003	0.950	1.000	0.523	0.002	0.004	0.556	1.000	0.825
%Fat[1]	0.001	0.009	0.881	0.002	0.006	0.790	0.007	0.006	0.219	-0.006	0.007	0.372	0.001	0.003	0.662	1.000	0.529	0.001	0.004	0.682	1.000	0.331
%SFA[1]	0.003	0.009	0.745	0.001	0.006	0.818	0.004	0.006	0.472	-0.004	0.006	0.522	0.001	0.003	0.744	1.000	0.806	0.001	0.004	0.827	1.000	0.627
%MFA[1]	0.005	0.009	0.560	-0.001	0.006	0.890	0.009	0.006	0.135	-0.008	0.007	0.261	0.001	0.003	0.671	1.000	0.298	0.001	0.004	0.830	1.000	0.176
%PFA[1]	-0.007	0.009	0.445	-4.70E-04	0.006	0.938	-0.001	0.006	0.908	-0.002	0.007	0.749	-0.002	0.003	0.573	1.000	0.942	-0.001	0.004	0.773	1.000	0.981
%Carbohydrate[1]	0.003	0.008	0.749	-4.60E-04	0.006	0.940	-0.008	0.006	0.158	0.005	0.007	0.481	-0.001	0.003	0.729	1.000	0.480	-0.002	0.004	0.610	1.000	0.327

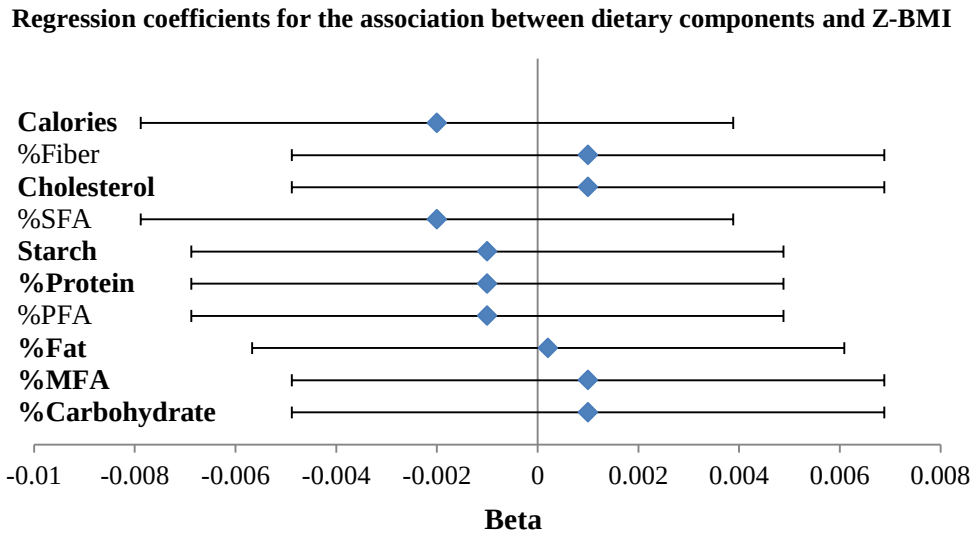
Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

Table 37: Interaction between weighted GRS and dietary factors on BMI

	SCHS cases			SCHS controls			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	$Q_{p\text{-}value}$	Beta	SE	P	P_{adjust}	$Q_{p\text{-}value}$
Calories	0.007	0.009	0.419	-0.005	0.006	0.407	-0.001	0.006	0.847	1.22E-04	0.007	0.985	-0.001	0.003	0.828	1.000	0.721	-0.002	0.004	0.555	1.000	0.828
Cholesterol	0.009	0.008	0.297	-2.90E-04	0.006	0.963	-0.004	0.006	0.496	-0.012	0.007	0.086	-0.003	0.003	0.426	1.000	0.275	-0.004	0.004	0.181	1.000	0.445
Starch	0.015	0.009	0.086	-2.90E-04	0.006	0.962	0.004	0.006	0.557	0.018	0.007	0.011	0.008	0.003	0.028	0.279	0.176	0.006	0.004	0.097	0.970	0.132
Fiber	-0.018	0.009	0.055	4.74E-04	0.006	0.938	-0.005	0.006	0.388	0.005	0.007	0.439	-0.002	0.003	0.440	1.000	0.215	-2.70E-04	0.004	0.940	1.000	0.510
%Protein[1]	-0.002	0.009	0.823	-0.007	0.006	0.268	0.007	0.006	0.219	-0.020	0.007	0.004	-0.005	0.003	0.162	1.000	**0.027**	-0.005	0.004	0.154	1.000	**0.011**
%Fat[1]	-0.017	0.009	0.056	0.002	0.006	0.796	-0.003	0.006	0.594	-0.019	0.007	0.004	-0.008	0.003	0.020	0.200	**0.078**	-0.006	0.004	0.086	0.860	**0.061**
%SFA[1]	-0.017	0.009	0.051	0.002	0.006	0.780	-2.50E-04	0.006	0.968	-0.011	0.007	0.118	-0.005	0.003	0.156	1.000	0.228	-0.003	0.004	0.471	1.000	0.366
%MFA[1]	-0.008	0.009	0.374	0.003	0.006	0.645	-0.001	0.006	0.803	-0.019	0.007	0.005	-0.005	0.003	0.105	1.000	**0.097**	-0.005	0.004	0.165	1.000	**0.044**
%PFA[1]	-0.012	0.009	0.196	0.006	0.006	0.326	-0.005	0.006	0.446	-0.013	0.007	0.058	-0.004	0.003	0.195	1.000	0.161	-0.003	0.004	0.383	1.000	0.111
%Carbohydrate[1]	0.012	0.009	0.175	0.001	0.006	0.852	-0.002	0.006	0.723	0.022	0.007	0.002	0.007	0.003	0.048	0.480	**0.044**	0.006	0.004	0.113	1.000	**0.021**

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

Figure 12: Regression coefficients for the associations between weighted GRS and Z-BMI adjusted for age, and sex.



None of the interaction remained statistically significant after adjusting for multiple testing (P<0.005=0.05/10 tests). Nominal evidence of interaction between wGRS with starch (β=0.008, SE=0.003, P=0.028), %fat (β=-0.008, SE=0.003, P=0.020) and %carbohydrate (β=-0.007, SE=0.003, P=0.048) on BMI was observed as shown in Table 37. In the case of %carbohydrate and starch intake, the association of the wGRS on BMI was stronger among individuals who consumed more starch / %carbohydrate as compared to individuals who had less intake of these two dietary components. While for %fat intake, the association of the wGRS on BMI was stronger among individuals who consumed less %fat.

6.3.6 Main effect of 64 SNPs on various dietary components

The association between the 64 SNPs and various dietary components was evaluated by linear regression with adjustment for age, gender and total calories intake (except using total calories as outcome). The analysis was conducted in each cohort

individually and subsequently meta-analyzed both in SCHS+SP2 and SCHS controls +SP2.

Results are summarized in Table 38 to Table 47. After meta-analysis, none of the association remained statistically significant after adjusting for multiple testing ($P<0.0007=0.05/74$ tests).

6.3.6.1 Total calories

After meta-analysis, rs1016287 on *FLJ30838* (β=-0.052, SE=0.025, P=0.034), rs3888190 on *ATP2A1* (β=-0.086, SE=0.038, P=0.026) and rs6804842 on *RARB* (β=0.074, SE=0.023, P=0.001) were found to be associated with total calories intake (Table 38). BMI risk allele T of rs1016287 and A of rs3888190 would decrease calories intake while G of rs6804842 increased intake of calories. In addition, if meta-analysis was conducted only in SCHS controls and SP2, the association between rs6804842 and total calories would still be significant after correction for multiple testing (β=0.091, SE=0.025, $P=3.11\times10^{-4}$, $P_{adjust}=0.023$).

6.3.6.2 Cholesterol

After meta-analysis, rs1000940 on *RABEP1* (β=0.049, SE=0.023, P=0.034) were found to be positively associated with cholesterol intake (Table 39). BMI risk allele G of rs1000940 would increase cholesterol intake.

Table 38: Association between 64 SNPs and calories intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	-0.007	0.054	0.901	-0.015	0.042	0.718	-0.034	0.041	0.401	0.017	0.046	0.704	-0.012	0.022	0.601	1.000	0.868	-0.013	0.025	0.604	1.000	0.701
2	rs1016287	-0.044	0.058	0.450	-0.068	0.045	0.131	-0.071	0.048	0.142	-0.021	0.049	0.666	-0.052	0.025	0.034	1.000	0.873	-0.054	0.027	0.047	1.000	0.714
3	rs10182181	0.010	0.053	0.855	-0.049	0.041	0.225	0.033	0.041	0.419	-0.079	0.044	0.071	-0.023	0.022	0.291	1.000	0.230	-0.030	0.024	0.213	1.000	0.147
4	rs10733682	0.004	0.059	0.947	0.055	0.048	0.257	0.004	0.046	0.937	0.024	0.054	0.650	0.023	0.026	0.373	1.000	0.871	0.027	0.028	0.340	1.000	0.746
5	rs10938397	0.067	0.058	0.253	-0.028	0.045	0.533	-0.023	0.046	0.622	0.062	0.050	0.214	0.012	0.025	0.627	1.000	0.354	1.47E-04	0.027	0.996	1.000	0.336
6	rs10968576	0.093	0.070	0.184	-0.009	0.054	0.864	0.046	0.053	0.383	0.017	0.059	0.774	0.031	0.029	0.282	1.000	0.686	0.018	0.032	0.564	1.000	0.763
7	rs11030104	0.056	0.050	0.267	0.003	0.039	0.941	-0.015	0.040	0.700	-0.032	0.043	0.464	-0.001	0.021	0.954	1.000	0.589	-0.014	0.023	0.562	1.000	0.838
8	rs11126666	0.067	0.056	0.233	-0.003	0.043	0.953	-0.027	0.045	0.544	0.013	0.048	0.792	0.007	0.024	0.777	1.000	0.617	-0.006	0.026	0.806	1.000	0.827
9	rs11191560	0.033	0.060	0.587	-0.012	0.046	0.788	0.044	0.045	0.322	0.012	0.051	0.817	0.018	0.025	0.459	1.000	0.836	0.015	0.027	0.571	1.000	0.674
10	rs11583200	0.018	0.086	0.830	-0.076	0.073	0.297	-0.008	0.076	0.917	-0.063	0.086	0.463	-0.034	0.040	0.389	1.000	0.815	-0.049	0.045	0.278	1.000	0.794
11	rs11688816	-0.036	0.057	0.530	0.004	0.045	0.926	-0.007	0.044	0.872	0.027	0.048	0.582	-0.001	0.024	0.976	1.000	0.866	0.007	0.026	0.797	1.000	0.873
12	rs12286929	-0.036	0.062	0.558	-0.023	0.045	0.606	-0.060	0.046	0.191	0.098	0.049	0.044	-0.005	0.025	0.844	1.000	0.095	0.001	0.027	0.969	1.000	**0.048**
13	rs12429545	0.043	0.062	0.481	-0.073	0.045	0.102	-0.034	0.047	0.465	0.098	0.053	0.066	-0.004	0.025	0.876	1.000	0.069	-0.013	0.028	0.627	1.000	**0.041**
14	rs12566985	-0.055	0.067	0.414	0.012	0.052	0.824	0.035	0.053	0.504	0.065	0.058	0.268	0.019	0.028	0.501	1.000	0.585	0.035	0.031	0.260	1.000	0.795
15	rs12940622	0.060	0.056	0.283	-0.001	0.044	0.988	-0.054	0.043	0.217	0.011	0.047	0.818	-0.003	0.023	0.910	1.000	0.437	-0.016	0.026	0.536	1.000	0.549
16	rs13021737	-0.089	0.103	0.384	0.006	0.076	0.941	0.032	0.075	0.667	0.129	0.088	0.144	0.026	0.042	0.536	1.000	0.440	0.049	0.046	0.287	1.000	0.552
17	rs13201877	-0.207	0.165	0.211	0.083	0.100	0.409	0.183	0.104	0.077	-0.142	0.115	0.216	0.023	0.057	0.692	1.000	**0.080**	0.054	0.061	0.376	1.000	0.102
18	rs1441264	-0.076	0.054	0.162	0.032	0.041	0.442	0.039	0.040	0.336	-0.075	0.045	0.092	-0.010	0.022	0.642	1.000	0.107	0.003	0.024	0.910	1.000	0.114
19	rs1460676	0.064	0.054	0.234	-0.058	0.042	0.170	0.044	0.041	0.281	0.077	0.045	0.089	0.027	0.022	0.227	1.000	0.116	0.019	0.025	0.434	1.000	**0.069**
20	rs1516725	-0.058	0.095	0.544	-0.096	0.079	0.223	0.061	0.072	0.394	-0.111	0.083	0.181	-0.043	0.040	0.290	1.000	0.353	-0.039	0.045	0.378	1.000	0.199
21	rs1528435	-0.042	0.058	0.463	-0.032	0.042	0.451	-0.023	0.043	0.589	-0.048	0.047	0.304	-0.035	0.023	0.131	1.000	0.982	-0.034	0.025	0.184	1.000	0.926
22	rs1558902	-0.086	0.074	0.250	0.031	0.060	0.605	0.079	0.063	0.210	-0.146	0.071	0.040	-0.017	0.033	0.602	1.000	**0.069**	-3.70E-04	0.037	0.992	1.000	**0.048**
23	rs16851483	-0.011	0.059	0.852	-0.034	0.047	0.460	-0.016	0.046	0.719	-0.057	0.051	0.267	-0.030	0.025	0.226	1.000	0.924	-0.034	0.028	0.211	1.000	0.841

Table 38 (Continued): Association between 64 SNPs and calories intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	0.023	0.055	0.677	0.005	0.039	0.899	0.066	0.041	0.110	-0.026	0.045	0.562	0.018	0.022	0.421	1.000	0.488	0.017	0.024	0.486	1.000	0.298
25	rs17203016	-0.027	0.079	0.735	0.054	0.058	0.355	-0.017	0.056	0.759	-0.173	0.063	0.006	-0.037	0.031	0.235	1.000	**0.063**	-0.039	0.034	0.252	1.000	**0.027**
26	rs17405819	-0.006	0.054	0.905	-0.004	0.041	0.928	-0.082	0.040	0.043	-0.054	0.044	0.224	-0.040	0.022	0.071	1.000	0.506	-0.047	0.024	0.054	1.000	0.392
27	rs17724992	-0.002	0.052	0.969	0.062	0.041	0.127	0.051	0.040	0.196	0.006	0.044	0.886	0.034	0.022	0.115	1.000	0.671	0.042	0.024	0.079	1.000	0.622
28	rs1928295	0.099	0.053	0.060	0.036	0.041	0.382	0.006	0.040	0.875	-0.069	0.045	0.123	0.013	0.022	0.559	1.000	**0.094**	-0.005	0.024	0.824	1.000	0.209
29	rs2033529	0.075	0.076	0.325	-0.026	0.056	0.641	-0.003	0.052	0.950	-0.011	0.058	0.854	1.39E-04	0.029	0.996	1.000	0.747	-0.013	0.032	0.685	1.000	0.955
30	rs2033732	0.110	0.052	0.034	-0.043	0.042	0.301	0.010	0.041	0.816	0.007	0.044	0.876	0.012	0.022	0.572	1.000	0.148	-0.009	0.024	0.704	1.000	0.604
31	rs205262	0.091	0.070	0.193	-0.035	0.057	0.537	0.051	0.060	0.396	-0.121	0.064	0.059	-0.007	0.031	0.814	1.000	**0.097**	-0.032	0.035	0.363	1.000	0.146
32	rs2075650	-0.028	0.097	0.772	0.131	0.074	0.074	0.018	0.071	0.796	0.097	0.079	0.216	0.062	0.039	0.112	1.000	0.504	0.080	0.043	0.062	1.000	0.522
33	rs2080454	-0.060	0.054	0.270	0.023	0.041	0.570	0.007	0.040	0.866	0.011	0.044	0.798	0.002	0.022	0.935	1.000	0.653	0.014	0.024	0.565	1.000	0.958
34	rs2112347	0.062	0.052	0.232	0.008	0.041	0.841	0.007	0.040	0.869	0.041	0.044	0.353	0.025	0.022	0.246	1.000	0.797	0.017	0.024	0.470	1.000	0.814
35	rs2176040	-0.147	0.100	0.142	-0.040	0.079	0.618	0.061	0.078	0.436	-0.086	0.083	0.303	-0.041	0.042	0.326	1.000	0.374	-0.019	0.046	0.687	1.000	0.415
36	rs2207139	-0.063	0.071	0.372	-0.166	0.059	0.005	-0.054	0.062	0.391	0.071	0.065	0.272	-0.058	0.032	0.067	1.000	**0.061**	-0.057	0.036	0.110	1.000	**0.025**
37	rs2287019	-0.028	0.065	0.672	-0.123	0.051	0.015	0.034	0.050	0.493	0.075	0.059	0.198	-0.014	0.028	0.602	1.000	**0.047**	-0.012	0.030	0.705	1.000	**0.019**
38	rs2365389	0.020	0.074	0.786	0.112	0.058	0.054	-0.055	0.064	0.391	-0.047	0.065	0.471	0.013	0.032	0.693	1.000	0.180	0.011	0.036	0.759	1.000	**0.087**
39	rs2820292	0.134	0.063	0.033	-0.023	0.053	0.660	-0.007	0.051	0.897	-0.078	0.055	0.152	-0.002	0.027	0.934	1.000	**0.078**	-0.035	0.030	0.257	1.000	0.610
40	rs2836754	-0.036	0.054	0.501	-0.003	0.041	0.946	-0.008	0.041	0.842	-0.066	0.046	0.153	-0.025	0.022	0.263	1.000	0.732	-0.023	0.025	0.356	1.000	0.539
41	rs29941	-0.045	0.066	0.495	0.066	0.048	0.169	0.048	0.050	0.345	-0.090	0.054	0.097	0.005	0.027	0.862	1.000	0.113	0.014	0.029	0.623	1.000	**0.071**
42	rs3101336	-0.033	0.099	0.739	0.013	0.074	0.862	-0.083	0.071	0.248	-0.021	0.084	0.801	-0.033	0.040	0.417	1.000	0.829	-0.032	0.044	0.459	1.000	0.643
43	rs3817334	0.057	0.057	0.313	-0.085	0.044	0.053	0.044	0.045	0.327	0.070	0.049	0.155	0.014	0.024	0.557	1.000	**0.060**	0.005	0.027	0.860	1.000	**0.035**
44	rs3849570	-0.030	0.051	0.561	-0.037	0.041	0.364	0.069	0.039	0.082	0.043	0.045	0.330	0.015	0.022	0.482	1.000	0.199	0.025	0.024	0.295	1.000	0.156
45	rs3888190	0.120	0.091	0.185	-0.047	0.072	0.516	-0.087	0.071	0.219	-0.282	0.078	3.23E-04	-0.086	0.038	0.026	1.000	**0.008**	-0.130	0.042	0.002	0.128	**0.064**
46	rs4256980	-0.045	0.055	0.409	-0.054	0.041	0.183	-0.050	0.041	0.221	0.009	0.045	0.836	-0.036	0.022	0.105	1.000	0.711	-0.034	0.024	0.160	1.000	0.511

Table 38 (Continued): Association between 64 SNPs and calories intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	-0.002	0.059	0.973	0.020	0.047	0.678	-0.041	0.045	0.366	-0.056	0.053	0.291	-0.020	0.025	0.425	1.000	0.689	-0.024	0.028	0.386	1.000	0.508
48	rs4787491	-0.030	0.053	0.575	0.004	0.039	0.922	0.020	0.041	0.614	-0.025	0.044	0.576	-0.004	0.022	0.857	1.000	0.836	0.001	0.024	0.957	1.000	0.751
49	rs492400	-0.083	0.066	0.208	-0.027	0.049	0.586	0.044	0.048	0.365	0.095	0.052	0.071	0.016	0.026	0.546	1.000	0.132	0.035	0.029	0.227	1.000	0.230
50	rs6567160	-0.028	0.072	0.692	0.006	0.053	0.911	-0.015	0.054	0.776	0.065	0.060	0.286	0.008	0.029	0.791	1.000	0.724	0.015	0.032	0.640	1.000	0.602
51	rs6804842	-0.006	0.055	0.907	0.119	0.043	0.006	0.036	0.043	0.402	0.120	0.045	0.008	0.074	0.023	0.001	0.074	0.169	0.091	0.025	3.11E-04	**0.023**	0.297
52	rs7138803	0.048	0.061	0.437	0.002	0.046	0.971	0.034	0.046	0.451	-0.064	0.051	0.215	0.004	0.025	0.884	1.000	0.441	-0.005	0.027	0.850	1.000	0.355
53	rs7141420	-0.051	0.052	0.325	0.059	0.040	0.144	-0.015	0.040	0.702	0.035	0.043	0.417	0.013	0.022	0.562	1.000	0.311	0.026	0.024	0.277	1.000	0.414
54	rs7164727	0.055	0.061	0.368	-0.082	0.046	0.073	-0.026	0.047	0.576	-0.066	0.050	0.183	-0.039	0.025	0.115	1.000	0.304	-0.058	0.027	0.033	1.000	0.682
55	rs7239883	0.140	0.056	0.013	0.007	0.043	0.880	0.001	0.043	0.978	-0.026	0.048	0.588	0.020	0.023	0.388	1.000	0.124	-0.005	0.026	0.853	1.000	0.868
56	rs7243357	-0.027	0.063	0.672	0.021	0.048	0.670	0.049	0.053	0.362	0.056	0.054	0.303	0.028	0.027	0.301	1.000	0.757	0.040	0.030	0.179	1.000	0.874
57	rs7599312	0.235	0.198	0.237	0.065	0.149	0.663	-0.233	0.123	0.059	0.015	0.157	0.922	-0.033	0.075	0.658	1.000	0.172	-0.078	0.081	0.336	1.000	0.239
58	rs7715256	0.121	0.137	0.378	0.108	0.109	0.323	-0.069	0.113	0.543	0.147	0.113	0.195	0.074	0.058	0.207	1.000	0.528	0.063	0.065	0.327	1.000	0.355
59	rs7903146	0.160	0.179	0.371	-0.369	0.125	0.003	-0.007	0.144	0.962	-0.139	0.149	0.353	-0.133	0.073	0.068	1.000	0.072	-0.191	0.080	0.017	1.000	0.151
60	rs9374842	0.031	0.097	0.751	0.092	0.069	0.180	0.049	0.071	0.491	-0.011	0.078	0.889	0.045	0.038	0.240	1.000	0.798	0.048	0.042	0.253	1.000	0.610
61	rs9400239	-0.008	0.058	0.890	-0.004	0.044	0.929	-0.033	0.044	0.447	-0.071	0.050	0.158	-0.029	0.024	0.229	1.000	0.763	-0.033	0.026	0.208	1.000	0.607
62	rs9641123	0.027	0.057	0.639	-0.022	0.043	0.615	0.029	0.043	0.506	0.047	0.047	0.317	0.018	0.023	0.436	1.000	0.726	0.016	0.026	0.520	1.000	0.526
63	rs977747	-0.068	0.143	0.634	-0.066	0.103	0.523	0.114	0.107	0.287	0.200	0.101	0.047	0.062	0.055	0.264	1.000	0.214	0.084	0.060	0.159	1.000	0.173
64	rs9914578	0.042	0.064	0.515	-0.009	0.049	0.847	0.005	0.051	0.918	0.032	0.056	0.572	0.013	0.027	0.620	1.000	0.908	0.007	0.030	0.808	1.000	0.857

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

Table 39: Association between 64 SNPs and cholesterol intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	0.017	0.059	0.781	0.079	0.044	0.074	0.027	0.041	0.518	0.066	0.047	0.158	0.049	0.023	0.034	1.000	0.755	0.055	0.025	0.029	1.000	0.660
2	rs1016287	0.015	0.064	0.818	-0.049	0.048	0.307	-0.030	0.049	0.541	0.019	0.050	0.699	-0.015	0.026	0.561	1.000	0.734	-0.021	0.028	0.460	1.000	0.601
3	rs10182181	-0.083	0.058	0.150	-0.050	0.043	0.246	0.068	0.042	0.104	-0.129	0.045	0.004	-0.041	0.023	0.075	1.000	**0.010**	-0.033	0.025	0.189	1.000	**0.005**
4	rs10733682	0.045	0.065	0.487	-0.035	0.051	0.493	-0.066	0.047	0.162	-0.005	0.055	0.925	-0.024	0.027	0.360	1.000	0.556	-0.039	0.029	0.188	1.000	0.704
5	rs10938397	0.037	0.064	0.566	0.011	0.048	0.816	-0.063	0.046	0.172	-0.018	0.051	0.725	-0.015	0.026	0.565	1.000	0.564	-0.024	0.028	0.381	1.000	0.528
6	rs10968576	0.014	0.077	0.855	0.052	0.057	0.363	0.055	0.054	0.304	0.041	0.060	0.499	0.044	0.030	0.142	1.000	0.975	0.050	0.033	0.129	1.000	0.983
7	rs11030104	-0.043	0.056	0.441	-0.016	0.041	0.704	0.055	0.040	0.173	0.082	0.044	0.063	0.026	0.022	0.240	1.000	0.197	0.039	0.024	0.106	1.000	0.239
8	rs11126666	-0.126	0.061	0.040	-0.047	0.046	0.302	0.005	0.045	0.907	0.017	0.049	0.723	-0.028	0.025	0.252	1.000	0.249	-0.009	0.027	0.731	1.000	0.581
9	rs11191560	0.043	0.066	0.515	-0.016	0.048	0.748	-0.019	0.045	0.677	-0.067	0.052	0.199	-0.020	0.026	0.433	1.000	0.628	-0.032	0.028	0.259	1.000	0.721
10	rs11583200	-0.004	0.094	0.970	-0.075	0.078	0.332	-0.127	0.076	0.098	-0.069	0.088	0.432	-0.075	0.042	0.070	1.000	0.793	-0.092	0.046	0.046	1.000	0.853
11	rs11688816	0.036	0.063	0.569	0.016	0.047	0.741	-0.084	0.044	0.060	0.015	0.050	0.764	-0.013	0.025	0.613	1.000	0.282	-0.022	0.027	0.426	1.000	0.211
12	rs12286929	0.038	0.068	0.579	-0.031	0.047	0.512	-0.009	0.047	0.849	0.033	0.050	0.509	0.002	0.026	0.927	1.000	0.752	-0.004	0.028	0.897	1.000	0.642
13	rs12429545	-0.063	0.068	0.356	0.034	0.047	0.477	0.063	0.048	0.188	-0.055	0.054	0.315	0.007	0.026	0.781	1.000	0.258	0.020	0.029	0.489	1.000	0.250
14	rs12566985	-0.037	0.074	0.616	0.050	0.055	0.368	-0.006	0.053	0.913	-0.025	0.060	0.678	4.24E-04	0.030	0.989	1.000	0.741	0.008	0.032	0.813	1.000	0.625
15	rs12940622	-0.085	0.062	0.168	0.054	0.047	0.244	0.007	0.044	0.874	0.008	0.048	0.864	0.006	0.025	0.811	1.000	0.354	0.023	0.027	0.391	1.000	0.713
16	rs13021737	-0.091	0.113	0.420	0.164	0.081	0.042	0.078	0.076	0.306	0.080	0.090	0.374	0.079	0.044	0.071	1.000	0.335	0.108	0.047	0.022	1.000	0.692
17	rs13201877	0.016	0.182	0.928	0.012	0.106	0.910	0.141	0.106	0.183	-0.073	0.117	0.534	0.031	0.060	0.598	1.000	0.592	0.033	0.063	0.598	1.000	0.387
18	rs1441264	-0.014	0.060	0.820	-0.017	0.044	0.704	-0.087	0.041	0.034	0.031	0.046	0.497	-0.026	0.023	0.253	1.000	0.278	-0.029	0.025	0.253	1.000	0.150
19	rs1460676	-0.059	0.059	0.320	0.006	0.044	0.888	0.033	0.041	0.423	1.57E-04	0.046	0.997	0.003	0.023	0.893	1.000	0.652	0.015	0.025	0.566	1.000	0.847
20	rs1516725	-0.198	0.104	0.057	-0.018	0.084	0.827	0.066	0.073	0.362	-0.044	0.085	0.605	-0.026	0.042	0.541	1.000	0.220	0.008	0.046	0.859	1.000	0.573
21	rs1528435	0.058	0.063	0.357	0.016	0.045	0.712	-0.036	0.044	0.418	-0.028	0.048	0.559	-0.005	0.024	0.851	1.000	0.584	-0.015	0.026	0.557	1.000	0.675
22	rs1558902	-0.076	0.082	0.353	-0.016	0.063	0.799	-0.027	0.064	0.676	-0.053	0.073	0.468	-0.038	0.035	0.269	1.000	0.939	-0.030	0.038	0.432	1.000	0.928
23	rs16851483	-0.055	0.064	0.391	0.051	0.050	0.305	0.079	0.046	0.091	-0.012	0.053	0.812	0.027	0.026	0.306	1.000	0.300	0.043	0.028	0.134	1.000	0.422

Table 39 (continued): Association between 64 SNPs and cholesterol intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	0.063	0.060	0.293	0.028	0.041	0.505	-0.031	0.042	0.451	0.046	0.046	0.309	0.020	0.023	0.387	1.000	0.492	0.012	0.025	0.617	1.000	0.407
25	rs17203016	-0.087	0.086	0.313	0.041	0.062	0.510	0.053	0.057	0.354	-0.002	0.065	0.974	0.016	0.033	0.632	1.000	0.555	0.033	0.035	0.353	1.000	0.805
26	rs17405819	-0.085	0.059	0.145	0.038	0.043	0.385	0.052	0.041	0.206	-0.068	0.045	0.133	-0.004	0.023	0.869	1.000	**0.081**	0.011	0.025	0.659	1.000	0.109
27	rs17724992	0.049	0.057	0.384	-0.005	0.043	0.912	0.035	0.040	0.377	0.006	0.045	0.900	0.019	0.023	0.394	1.000	0.840	0.014	0.025	0.583	1.000	0.777
28	rs1928295	0.019	0.058	0.742	-0.019	0.044	0.665	0.025	0.040	0.535	0.091	0.046	0.049	0.028	0.023	0.216	1.000	0.385	0.030	0.025	0.228	1.000	0.221
29	rs2033529	0.116	0.084	0.168	0.025	0.059	0.677	-0.050	0.052	0.337	0.026	0.060	0.667	0.012	0.031	0.706	1.000	0.385	-0.004	0.033	0.893	1.000	0.532
30	rs2033732	-0.105	0.057	0.065	0.007	0.044	0.869	0.033	0.042	0.426	-0.086	0.045	0.057	-0.028	0.023	0.232	1.000	**0.099**	-0.012	0.025	0.625	1.000	0.133
31	rs205262	0.005	0.077	0.951	-0.070	0.061	0.246	0.071	0.061	0.242	-0.001	0.066	0.992	0.001	0.033	0.978	1.000	0.437	3.29E-05	0.036	0.999	1.000	0.257
32	rs2075650	-0.157	0.106	0.139	-0.078	0.078	0.321	0.038	0.072	0.593	0.089	0.081	0.273	-0.009	0.041	0.818	1.000	0.202	0.016	0.044	0.712	1.000	0.310
33	rs2080454	0.028	0.060	0.638	0.013	0.043	0.770	-0.028	0.041	0.488	0.005	0.045	0.920	-6.73E-05	0.023	0.998	1.000	0.850	-0.005	0.025	0.843	1.000	0.764
34	rs2112347	0.060	0.057	0.292	0.011	0.043	0.792	0.017	0.041	0.675	0.012	0.045	0.797	0.021	0.023	0.355	1.000	0.903	0.014	0.025	0.584	1.000	0.994
35	rs2176040	0.050	0.110	0.649	0.004	0.084	0.965	0.006	0.079	0.941	0.050	0.086	0.558	0.024	0.044	0.585	1.000	0.967	0.019	0.048	0.691	1.000	0.908
36	rs2207139	-0.023	0.078	0.765	-0.030	0.062	0.631	0.014	0.063	0.820	0.018	0.066	0.782	-0.004	0.033	0.901	1.000	0.933	1.02E-04	0.037	0.998	1.000	0.836
37	rs2287019	-0.053	0.072	0.459	0.029	0.054	0.586	0.131	0.051	0.010	0.037	0.060	0.535	0.050	0.029	0.080	1.000	0.189	0.070	0.031	0.025	1.000	0.318
38	rs2365389	-0.022	0.081	0.783	-0.060	0.062	0.328	0.028	0.064	0.666	0.021	0.067	0.755	-0.009	0.034	0.789	1.000	0.742	-0.006	0.037	0.867	1.000	0.545
39	rs2820292	-0.073	0.069	0.291	-0.002	0.056	0.974	-0.054	0.051	0.292	0.023	0.056	0.686	-0.024	0.029	0.406	1.000	0.636	-0.014	0.031	0.664	1.000	0.581
40	rs2836754	-0.011	0.059	0.855	-0.067	0.044	0.125	-0.051	0.041	0.215	-0.005	0.047	0.918	-0.038	0.023	0.101	1.000	0.741	-0.043	0.025	0.088	1.000	0.607
41	rs29941	0.018	0.073	0.803	-0.019	0.051	0.711	-0.022	0.051	0.671	0.023	0.056	0.682	-0.004	0.028	0.893	1.000	0.912	-0.008	0.030	0.803	1.000	0.809
42	rs3101336	-0.123	0.108	0.257	-0.161	0.079	0.040	-0.046	0.072	0.521	0.013	0.086	0.877	-0.076	0.042	0.068	1.000	0.455	-0.068	0.045	0.132	1.000	0.301
43	rs3817334	-0.037	0.063	0.549	0.016	0.047	0.731	0.004	0.046	0.933	0.023	0.050	0.649	0.005	0.025	0.828	1.000	0.886	0.014	0.027	0.617	1.000	0.960
44	rs3849570	-0.064	0.057	0.264	0.055	0.043	0.198	0.037	0.040	0.356	0.012	0.046	0.792	0.020	0.023	0.377	1.000	0.384	0.036	0.025	0.147	1.000	0.786
45	rs3888190	-0.019	0.100	0.847	0.001	0.076	0.986	-0.028	0.072	0.701	0.094	0.081	0.246	0.012	0.040	0.769	1.000	0.694	0.018	0.044	0.685	1.000	0.513
46	rs4256980	0.035	0.060	0.559	-0.035	0.043	0.425	0.015	0.041	0.709	-0.023	0.046	0.609	-0.006	0.023	0.801	1.000	0.725	-0.013	0.025	0.606	1.000	0.680

Table 39 (continued): Association between 64 SNPs and cholesterol intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	-0.136	0.065	0.036	0.013	0.050	0.796	0.058	0.046	0.207	0.046	0.054	0.397	0.011	0.026	0.681	1.000	**0.085**	0.040	0.029	0.166	1.000	0.796
48	rs4787491	0.015	0.058	0.802	0.041	0.042	0.325	-0.001	0.041	0.981	-0.086	0.045	0.059	-0.007	0.023	0.747	1.000	0.213	-0.011	0.025	0.648	1.000	0.115
49	rs492400	0.073	0.072	0.317	-0.068	0.052	0.188	-0.017	0.049	0.725	-0.019	0.054	0.721	-0.019	0.027	0.484	1.000	0.476	-0.035	0.030	0.244	1.000	0.732
50	rs6567160	0.081	0.079	0.306	0.056	0.056	0.317	0.015	0.055	0.783	-0.097	0.062	0.119	0.010	0.031	0.742	1.000	0.216	-0.002	0.033	0.941	1.000	0.173
51	rs6804842	-0.021	0.060	0.731	0.048	0.046	0.291	0.002	0.044	0.956	-0.016	0.047	0.726	0.006	0.024	0.789	1.000	0.732	0.012	0.026	0.659	1.000	0.592
52	rs7138803	0.010	0.067	0.882	0.013	0.049	0.791	-0.004	0.046	0.934	-0.004	0.053	0.935	0.003	0.026	0.911	1.000	0.993	0.002	0.028	0.953	1.000	0.961
53	rs7141420	0.016	0.057	0.774	0.002	0.043	0.953	0.028	0.041	0.494	0.056	0.044	0.209	0.026	0.023	0.245	1.000	0.854	0.028	0.025	0.254	1.000	0.689
54	rs7164727	-0.125	0.066	0.059	-0.057	0.048	0.240	-0.008	0.047	0.863	0.072	0.051	0.154	-0.019	0.026	0.460	1.000	**0.090**	6.97E-05	0.028	0.998	1.000	0.179
55	rs7239883	0.010	0.062	0.877	-0.014	0.046	0.756	-0.025	0.043	0.568	-0.034	0.049	0.492	-0.019	0.024	0.442	1.000	0.954	-0.024	0.026	0.368	1.000	0.958
56	rs7243357	0.199	0.069	0.004	-0.036	0.051	0.482	0.070	0.054	0.198	-0.070	0.055	0.203	0.023	0.028	0.417	1.000	**0.010**	-0.012	0.031	0.686	1.000	0.164
57	rs7599312	0.286	0.218	0.191	0.060	0.158	0.707	-0.162	0.125	0.196	-0.407	0.160	0.011	-0.109	0.078	0.162	1.000	**0.045**	-0.167	0.084	0.046	1.000	0.116
58	rs7715256	-0.037	0.151	0.805	-0.080	0.115	0.486	-0.133	0.115	0.246	-0.021	0.116	0.855	-0.072	0.061	0.238	1.000	0.911	-0.079	0.067	0.238	1.000	0.790
59	rs7903146	0.356	0.197	0.071	-0.211	0.135	0.119	-0.233	0.146	0.110	-0.029	0.153	0.848	-0.086	0.077	0.263	1.000	**0.070**	-0.164	0.083	0.048	1.000	0.571
60	rs9374842	-0.309	0.106	0.004	0.049	0.073	0.498	-0.008	0.072	0.907	-0.011	0.080	0.889	-0.035	0.040	0.387	1.000	**0.040**	0.011	0.043	0.799	1.000	0.808
61	rs9400239	0.059	0.063	0.355	-0.007	0.047	0.875	0.003	0.044	0.949	0.061	0.051	0.235	0.023	0.025	0.369	1.000	0.684	0.016	0.027	0.562	1.000	0.575
62	rs9641123	0.047	0.062	0.448	0.024	0.046	0.597	-0.068	0.043	0.116	-0.098	0.048	0.043	-0.032	0.024	0.186	1.000	0.128	-0.046	0.026	0.079	1.000	0.152
63	rs977747	-0.208	0.157	0.187	-0.100	0.110	0.366	0.103	0.108	0.340	-0.140	0.103	0.173	-0.070	0.057	0.225	1.000	0.276	-0.048	0.062	0.433	1.000	0.226
64	rs9914578	0.034	0.071	0.629	-0.001	0.052	0.980	0.023	0.051	0.653	0.038	0.058	0.512	0.021	0.028	0.453	1.000	0.959	0.019	0.031	0.543	1.000	0.876

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

6.3.6.3 Starch

After meta-analysis, rs205262 on *C6orf106* (β=0.070, SE=0.032, P=0.031) were found to be positively associated with starch intake (Table 40). BMI risk allele G of rs205262 would increase starch intake.

6.3.6.4 Fiber

After meta-analysis, nominal significance were found between rs1000940 on *RABEP1* (β=-0.061, SE=0.023, P=0.008), rs1016287 on *FLJ30838* (β=-0.070, SE=0.026, P=0.006), rs10968576 on *LINGO* (β=-0.061, SE=0.030, P=0.042), rs11030104 on *BDNF* (β=-0.048, SE=0.022, P=0.030), rs1928295 on *TLR4* (β=-0.049, SE=0.023, P=0.031) and rs9374842 on *LOC285762* (β=-0.079, SE=0.040, P=0.046) and fiber intake (Table 41). BMI risk allele G of rs1000940, T of rs1016287, G of rs10968576, A of rs11030104, T of rs1928295 and T of rs9374842 were all negatively associated with dietary fiber intake.

6.3.6.5 %Protein

After meta-analysis, rs2287019 on *QPCTL* (β=0.057, SE=0.029, P=0.047), rs2365389 on *FHIT* (β=-0.070, SE=0.034, P=0.037) and rs3101336 on *NEGR1* (β=-0.123, SE=0.042, P=0.003) were found to be associated with %protein intake (Table 42). BMI risk allele C of rs2287019 was positively associated while C of rs2365389 and C of rs3101336 were negatively associated with %protein intake.

Table 40: Association between 64 SNPs and starch intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	-0.014	0.059	0.819	-0.053	0.044	0.231	-0.003	0.041	0.939	0.046	0.047	0.322	-0.006	0.023	0.783	1.000	0.494	-0.005	0.025	0.840	1.000	0.304
2	rs1016287	0.008	0.064	0.899	0.012	0.048	0.804	0.016	0.049	0.749	0.002	0.050	0.964	0.010	0.026	0.706	1.000	0.998	0.010	0.028	0.721	1.000	0.981
3	rs10182181	-0.043	0.058	0.459	0.054	0.043	0.216	0.020	0.042	0.639	-0.023	0.045	0.614	0.008	0.023	0.717	1.000	0.489	0.018	0.025	0.476	1.000	0.472
4	rs10733682	-0.155	0.065	0.017	-0.081	0.051	0.108	-0.003	0.047	0.950	-0.047	0.055	0.399	-0.060	0.027	0.024	1.000	0.274	-0.041	0.029	0.159	1.000	0.518
5	rs10938397	0.014	0.064	0.827	0.076	0.047	0.109	-0.033	0.046	0.481	0.081	0.051	0.118	0.034	0.026	0.179	1.000	0.287	0.038	0.028	0.171	1.000	0.161
6	rs10968576	0.054	0.077	0.486	-0.035	0.056	0.540	-0.038	0.053	0.471	0.084	0.060	0.162	0.007	0.030	0.810	1.000	0.351	-0.001	0.033	0.972	1.000	0.241
7	rs11030104	0.036	0.056	0.515	0.053	0.041	0.200	-0.085	0.040	0.035	-0.028	0.044	0.530	-0.012	0.022	0.594	1.000	**0.085**	-0.021	0.024	0.389	1.000	**0.056**
8	rs11126666	0.132	0.061	0.031	-0.014	0.046	0.760	0.060	0.045	0.183	0.050	0.049	0.314	0.048	0.025	0.053	1.000	0.284	0.031	0.027	0.244	1.000	0.465
9	rs11191560	-0.064	0.066	0.335	-0.002	0.048	0.974	0.016	0.045	0.723	-0.037	0.052	0.479	-0.014	0.026	0.589	1.000	0.737	-0.005	0.028	0.859	1.000	0.743
10	rs11583200	-0.015	0.094	0.875	0.104	0.077	0.177	0.133	0.076	0.081	-0.082	0.088	0.348	0.048	0.041	0.245	1.000	0.219	0.063	0.046	0.170	1.000	0.144
11	rs11688816	-0.025	0.063	0.684	0.025	0.047	0.600	-0.004	0.044	0.927	0.028	0.049	0.564	0.009	0.025	0.724	1.000	0.883	0.015	0.027	0.575	1.000	0.860
12	rs12286929	0.122	0.067	0.071	-0.073	0.047	0.124	-0.044	0.047	0.353	-0.079	0.050	0.115	-0.038	0.026	0.143	1.000	**0.077**	-0.064	0.028	0.020	1.000	0.855
13	rs12429545	0.004	0.068	0.954	0.087	0.047	0.066	-0.060	0.048	0.210	0.045	0.054	0.411	0.020	0.026	0.450	1.000	0.167	0.023	0.029	0.426	1.000	**0.082**
14	rs12566985	0.066	0.073	0.370	-0.117	0.055	0.033	-0.096	0.053	0.070	0.046	0.060	0.444	-0.042	0.029	0.159	1.000	**0.065**	-0.062	0.032	0.053	1.000	**0.097**
15	rs12940622	0.047	0.062	0.450	0.012	0.046	0.795	-0.025	0.044	0.567	0.071	0.048	0.144	0.021	0.024	0.392	1.000	0.500	0.016	0.027	0.544	1.000	0.340
16	rs13021737	-0.081	0.113	0.472	-0.116	0.080	0.150	0.017	0.076	0.827	-0.113	0.090	0.209	-0.067	0.043	0.124	1.000	0.602	-0.064	0.047	0.172	1.000	0.399
17	rs13201877	0.175	0.182	0.335	0.024	0.106	0.823	0.014	0.106	0.898	-0.011	0.117	0.927	0.028	0.059	0.640	1.000	0.852	0.010	0.063	0.873	1.000	0.976
18	rs1441264	0.015	0.060	0.805	0.017	0.043	0.691	-0.003	0.041	0.933	0.019	0.046	0.680	0.011	0.023	0.641	1.000	0.981	0.010	0.025	0.687	1.000	0.917
19	rs1460676	-0.005	0.059	0.937	-0.079	0.044	0.076	0.065	0.041	0.113	-0.030	0.046	0.514	-0.009	0.023	0.695	1.000	0.114	-0.010	0.025	0.695	1.000	**0.051**
20	rs1516725	0.007	0.104	0.949	0.014	0.083	0.863	-0.055	0.072	0.443	0.082	0.085	0.331	0.006	0.042	0.880	1.000	0.672	0.006	0.046	0.891	1.000	0.462
21	rs1528435	-0.084	0.063	0.182	-0.025	0.045	0.568	-0.004	0.044	0.934	-0.024	0.048	0.615	-0.027	0.024	0.262	1.000	0.773	-0.017	0.026	0.510	1.000	0.928
22	rs1558902	0.069	0.082	0.399	-0.071	0.063	0.264	-0.020	0.064	0.755	0.003	0.073	0.971	-0.014	0.035	0.683	1.000	0.594	-0.032	0.038	0.399	1.000	0.727
23	rs16851483	-0.066	0.064	0.302	-0.075	0.049	0.129	0.009	0.046	0.846	-0.068	0.052	0.197	-0.045	0.026	0.080	1.000	0.568	-0.041	0.028	0.145	1.000	0.388

Table 40 (continued): Association between 64 SNPs and starch intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	0.064	0.059	0.279	0.007	0.041	0.873	0.011	0.041	0.795	0.009	0.046	0.841	0.017	0.023	0.455	1.000	0.861	0.009	0.025	0.720	1.000	0.997
25	rs17203016	-0.039	0.086	0.651	0.040	0.062	0.517	0.065	0.057	0.253	0.050	0.064	0.434	0.040	0.033	0.223	1.000	0.788	0.053	0.035	0.134	1.000	0.956
26	rs17405819	0.058	0.059	0.324	0.016	0.043	0.706	-0.015	0.041	0.714	-0.004	0.045	0.935	0.008	0.023	0.736	1.000	0.766	-0.001	0.025	0.960	1.000	0.869
27	rs17724992	-0.008	0.057	0.893	-0.084	0.043	0.051	0.053	0.040	0.186	0.056	0.045	0.220	0.006	0.023	0.779	1.000	**0.072**	0.009	0.025	0.716	1.000	**0.031**
28	rs1928295	-0.038	0.058	0.517	0.038	0.043	0.382	0.006	0.040	0.889	0.040	0.046	0.385	0.016	0.023	0.475	1.000	0.693	0.026	0.025	0.292	1.000	0.807
29	rs2033529	-0.026	0.084	0.758	0.036	0.059	0.534	0.087	0.052	0.094	-0.091	0.059	0.126	0.012	0.030	0.684	1.000	0.141	0.018	0.033	0.578	1.000	**0.073**
30	rs2033732	-0.003	0.057	0.954	0.002	0.044	0.968	-0.059	0.041	0.153	-0.001	0.045	0.984	-0.019	0.023	0.420	1.000	0.706	-0.021	0.025	0.393	1.000	0.519
31	rs205262	0.071	0.077	0.356	0.044	0.060	0.462	0.032	0.060	0.600	0.144	0.065	0.028	0.070	0.032	0.031	1.000	0.603	0.070	0.036	0.051	1.000	0.395
32	rs2075650	0.097	0.106	0.361	0.032	0.078	0.683	-0.076	0.071	0.291	-0.081	0.081	0.315	-0.022	0.041	0.585	1.000	0.418	-0.043	0.044	0.332	1.000	0.508
33	rs2080454	-0.008	0.060	0.887	0.063	0.043	0.140	-0.013	0.040	0.756	0.028	0.045	0.535	0.020	0.023	0.384	1.000	0.588	0.025	0.025	0.317	1.000	0.435
34	rs2112347	0.057	0.057	0.316	-0.022	0.043	0.606	-0.010	0.041	0.809	0.097	0.045	0.032	0.024	0.023	0.285	1.000	0.188	0.018	0.025	0.466	1.000	0.111
35	rs2176040	-0.077	0.110	0.485	-0.113	0.083	0.175	0.011	0.079	0.886	-0.131	0.085	0.125	-0.074	0.044	0.089	1.000	0.608	-0.074	0.048	0.122	1.000	0.400
36	rs2207139	-0.001	0.079	0.992	-0.003	0.062	0.963	0.057	0.063	0.370	0.006	0.066	0.923	0.016	0.033	0.622	1.000	0.903	0.020	0.037	0.583	1.000	0.773
37	rs2287019	-0.071	0.072	0.321	-0.035	0.054	0.515	-0.026	0.051	0.613	0.062	0.060	0.308	-0.016	0.029	0.583	1.000	0.492	-0.005	0.031	0.870	1.000	0.428
38	rs2365389	-0.120	0.081	0.142	0.001	0.061	0.992	-0.012	0.065	0.850	0.063	0.066	0.341	-0.007	0.034	0.830	1.000	0.383	0.016	0.037	0.665	1.000	0.685
39	rs2820292	0.024	0.069	0.733	0.101	0.056	0.070	-0.034	0.051	0.500	0.027	0.056	0.624	0.027	0.028	0.347	1.000	0.359	0.027	0.031	0.380	1.000	0.200
40	rs2836754	0.020	0.059	0.738	0.020	0.044	0.645	-0.041	0.041	0.317	-0.112	0.047	0.018	-0.032	0.023	0.173	1.000	0.163	-0.041	0.025	0.105	1.000	0.121
41	rs29941	-0.009	0.073	0.904	-0.025	0.051	0.625	0.069	0.051	0.177	-0.053	0.056	0.343	-0.001	0.028	0.963	1.000	0.396	5.79E-07	0.030	1.000	1.000	0.227
42	rs3101336	-0.064	0.109	0.558	0.121	0.078	0.123	-0.042	0.072	0.558	-0.015	0.086	0.862	0.007	0.042	0.862	1.000	0.381	0.019	0.045	0.666	1.000	0.277
43	rs3817334	0.072	0.062	0.248	-0.009	0.046	0.844	-0.032	0.046	0.481	-0.033	0.050	0.511	-0.009	0.025	0.721	1.000	0.536	-0.024	0.027	0.371	1.000	0.920
44	rs3849570	-0.024	0.057	0.669	-0.048	0.043	0.256	0.009	0.040	0.822	0.004	0.046	0.926	-0.014	0.023	0.549	1.000	0.759	-0.011	0.025	0.640	1.000	0.568
45	rs3888190	-0.024	0.100	0.810	0.078	0.076	0.306	0.077	0.071	0.281	0.043	0.081	0.593	0.053	0.040	0.189	1.000	0.843	0.067	0.044	0.124	1.000	0.938
46	rs4256980	-0.015	0.060	0.803	-0.010	0.043	0.823	0.016	0.041	0.700	-0.025	0.046	0.591	-0.006	0.023	0.786	1.000	0.924	-0.005	0.025	0.849	1.000	0.797

Table 40 (continued): Association between 64 SNPs and starch intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	0.154	0.064	0.017	0.050	0.050	0.321	-0.052	0.046	0.254	-0.053	0.054	0.329	0.01	0.026	0.715	1.000	**0.032**	-0.019	0.029	0.509	1.000	0.246
48	rs4787491	0.014	0.058	0.805	0.008	0.041	0.844	0.011	0.041	0.790	0.021	0.045	0.642	0.013	0.023	0.561	1.000	0.997	0.013	0.024	0.599	1.000	0.976
49	rs492400	0.091	0.072	0.208	0.064	0.051	0.211	0.049	0.049	0.320	-0.010	0.054	0.855	0.044	0.027	0.108	1.000	0.661	0.036	0.030	0.221	1.000	0.578
50	rs6567160	-0.057	0.079	0.471	0.043	0.055	0.436	0.020	0.055	0.714	0.034	0.062	0.587	0.019	0.030	0.536	1.000	0.759	0.032	0.033	0.330	1.000	0.957
51	rs6804842	-0.051	0.060	0.398	-0.030	0.045	0.504	-0.027	0.044	0.532	0.092	0.046	0.048	-1.97E-04	0.024	0.993	1.000	0.141	0.009	0.026	0.721	1.000	**0.099**
52	rs7138803	0.056	0.067	0.404	-0.035	0.049	0.469	0.025	0.046	0.582	0.013	0.053	0.799	0.010	0.026	0.710	1.000	0.693	0.001	0.028	0.959	1.000	0.641
53	rs7141420	-0.020	0.057	0.727	-0.075	0.042	0.077	0.006	0.041	0.880	-0.046	0.044	0.296	-0.034	0.022	0.127	1.000	0.564	-0.037	0.024	0.131	1.000	0.375
54	rs7164727	0.057	0.067	0.394	-0.021	0.048	0.656	0.050	0.047	0.292	0.014	0.051	0.777	0.021	0.026	0.417	1.000	0.693	0.015	0.028	0.601	1.000	0.573
55	rs7239883	0.023	0.062	0.708	0.017	0.045	0.707	-0.017	0.043	0.701	0.021	0.049	0.663	0.008	0.024	0.728	1.000	0.919	0.006	0.026	0.826	1.000	0.806
56	rs7243357	-0.087	0.069	0.213	-0.007	0.051	0.898	-0.109	0.054	0.043	-0.030	0.055	0.582	-0.054	0.028	0.055	1.000	0.510	-0.047	0.031	0.123	1.000	0.359
57	rs7599312	-0.048	0.218	0.825	0.008	0.157	0.958	-0.203	0.125	0.106	0.058	0.160	0.716	-0.069	0.078	0.377	1.000	0.568	-0.072	0.084	0.389	1.000	0.366
58	rs7715256	0.216	0.150	0.151	-0.050	0.115	0.666	-0.045	0.115	0.695	0.063	0.116	0.588	0.026	0.061	0.668	1.000	0.472	-0.011	0.066	0.868	1.000	0.739
59	rs7903146	-0.248	0.197	0.207	0.075	0.133	0.575	0.148	0.145	0.308	0.087	0.154	0.575	0.049	0.076	0.518	1.000	0.416	0.102	0.083	0.218	1.000	0.927
60	rs9374842	0.231	0.106	0.030	-0.012	0.072	0.867	-0.029	0.071	0.687	-0.062	0.079	0.436	0.004	0.040	0.914	1.000	0.138	-0.033	0.043	0.447	1.000	0.896
61	rs9400239	-0.132	0.063	0.037	0.046	0.047	0.324	0.041	0.044	0.362	-0.039	0.051	0.450	-0.004	0.025	0.878	1.000	**0.082**	0.020	0.027	0.463	1.000	0.399
62	rs9641123	-0.093	0.062	0.136	0.030	0.045	0.513	-0.032	0.043	0.460	-0.024	0.048	0.621	-0.022	0.024	0.372	1.000	0.449	-0.009	0.026	0.734	1.000	0.576
63	rs977747	0.225	0.157	0.153	0.149	0.109	0.173	0.026	0.108	0.813	0.105	0.103	0.307	0.111	0.057	0.053	1.000	0.736	0.093	0.061	0.129	1.000	0.717
64	rs9914578	-0.137	0.070	0.052	0.042	0.052	0.422	0.011	0.051	0.836	0.044	0.058	0.450	0.004	0.028	0.888	1.000	0.170	0.031	0.031	0.315	1.000	0.884

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

Table 41: Association between 64 SNPs and fiber intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	-0.057	0.059	0.339	-0.096	0.044	0.029	-0.048	0.040	0.235	-0.042	0.046	0.366	-0.061	0.023	0.008	0.512	0.822	-0.062	0.025	0.014	0.896	0.635
2	rs1016287	-0.061	0.064	0.338	-0.104	0.048	0.030	-0.073	0.048	0.130	-0.036	0.049	0.472	-0.070	0.026	0.006	0.384	0.799	-0.072	0.028	0.010	0.640	0.610
3	rs10182181	0.049	0.058	0.395	0.007	0.044	0.874	0.018	0.041	0.667	-0.017	0.044	0.694	0.010	0.023	0.651	1.000	0.829	0.003	0.025	0.899	1.000	0.840
4	rs10733682	0.078	0.065	0.232	0.020	0.051	0.696	0.057	0.046	0.219	0.042	0.054	0.446	0.047	0.026	0.078	1.000	0.904	0.041	0.029	0.162	1.000	0.866
5	rs10938397	-0.018	0.065	0.778	-0.030	0.048	0.522	-0.008	0.046	0.862	-0.068	0.051	0.184	-0.031	0.025	0.224	1.000	0.848	-0.033	0.028	0.230	1.000	0.683
6	rs10968576	-0.133	0.077	0.085	0.003	0.057	0.959	-0.089	0.053	0.092	-0.052	0.059	0.385	-0.061	0.030	0.042	1.000	0.483	-0.048	0.032	0.140	1.000	0.491
7	rs11030104	-0.091	0.056	0.104	-0.056	0.041	0.179	-0.012	0.040	0.769	-0.056	0.044	0.201	-0.048	0.022	0.030	1.000	0.686	-0.040	0.024	0.097	1.000	0.679
8	rs11126666	0.026	0.062	0.677	-0.026	0.046	0.565	-0.026	0.045	0.562	-0.025	0.049	0.611	-0.018	0.025	0.474	1.000	0.899	-0.026	0.027	0.336	1.000	1.000
9	rs11191560	0.037	0.066	0.573	0.083	0.048	0.086	-0.012	0.045	0.786	0.048	0.052	0.349	0.037	0.026	0.151	1.000	0.540	0.037	0.028	0.187	1.000	0.340
10	rs11583200	0.114	0.094	0.227	-0.047	0.077	0.547	0.062	0.075	0.414	-0.010	0.087	0.912	0.025	0.041	0.547	1.000	0.543	0.004	0.046	0.935	1.000	0.596
11	rs11688816	0.002	0.063	0.974	-0.070	0.047	0.137	-0.021	0.044	0.628	-0.036	0.049	0.464	-0.035	0.025	0.159	1.000	0.800	-0.042	0.027	0.122	1.000	0.741
12	rs12286929	-0.072	0.068	0.290	0.084	0.047	0.076	0.032	0.046	0.491	0.033	0.049	0.511	0.032	0.025	0.202	1.000	0.314	0.049	0.027	0.071	1.000	0.673
13	rs12429545	0.099	0.068	0.147	-0.076	0.047	0.108	-0.048	0.047	0.305	0.114	0.054	0.034	0.003	0.026	0.897	1.000	**0.017**	-0.013	0.028	0.643	1.000	**0.019**
14	rs12566985	-0.084	0.074	0.254	0.070	0.055	0.203	-0.002	0.053	0.967	-0.014	0.059	0.807	0.002	0.029	0.937	1.000	0.394	0.019	0.032	0.561	1.000	0.510
15	rs12940622	0.032	0.062	0.604	-0.041	0.047	0.382	0.012	0.044	0.789	-0.005	0.048	0.915	-0.004	0.024	0.874	1.000	0.779	-0.010	0.026	0.694	1.000	0.707
16	rs13021737	0.196	0.113	0.083	-0.048	0.081	0.550	-0.002	0.075	0.983	-0.100	0.089	0.264	-0.009	0.043	0.831	1.000	0.206	-0.044	0.047	0.343	1.000	0.701
17	rs13201877	-0.048	0.182	0.792	-0.059	0.106	0.575	-0.064	0.105	0.538	-0.069	0.115	0.549	-0.062	0.059	0.292	1.000	1.000	-0.064	0.063	0.305	1.000	0.998
18	rs1441264	0.011	0.060	0.859	-0.032	0.043	0.465	0.044	0.040	0.276	0.045	0.045	0.319	0.018	0.023	0.421	1.000	0.552	0.020	0.025	0.425	1.000	0.354
19	rs1460676	0.006	0.059	0.924	0.058	0.045	0.192	-0.037	0.041	0.362	0.080	0.046	0.078	0.025	0.023	0.276	1.000	0.216	0.029	0.025	0.253	1.000	0.115
20	rs1516725	0.030	0.106	0.779	-0.114	0.083	0.171	0.015	0.072	0.835	0.053	0.084	0.529	-0.006	0.042	0.888	1.000	0.498	-0.013	0.046	0.784	1.000	0.326
21	rs1528435	0.062	0.062	0.321	-0.006	0.045	0.894	0.013	0.043	0.759	0.040	0.047	0.392	0.022	0.024	0.360	1.000	0.803	0.015	0.026	0.563	1.000	0.775
22	rs1558902	0.004	0.082	0.960	0.123	0.063	0.052	-0.107	0.063	0.090	0.027	0.072	0.704	0.012	0.034	0.733	1.000	0.082	0.013	0.038	0.725	1.000	**0.035**
23	rs16851483	0.076	0.064	0.240	0.037	0.049	0.456	0.090	0.046	0.051	-0.018	0.052	0.724	0.046	0.026	0.074	1.000	0.441	0.040	0.028	0.151	1.000	0.295

Table 41 (continued): Association between 64 SNPs and fiber intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	0.012	0.061	0.840	-0.015	0.041	0.715	0.005	0.041	0.899	-0.037	0.045	0.407	-0.011	0.023	0.636	1.000	0.884	-0.015	0.025	0.553	1.000	0.784
25	rs17203016	-0.070	0.087	0.420	-0.049	0.062	0.427	0.032	0.056	0.576	-0.069	0.064	0.278	-0.031	0.032	0.343	1.000	0.599	-0.024	0.035	0.485	1.000	0.441
26	rs17405819	0.053	0.059	0.370	-0.029	0.043	0.506	0.009	0.041	0.819	0.022	0.045	0.618	0.009	0.023	0.703	1.000	0.705	0.001	0.025	0.972	1.000	0.690
27	rs17724992	0.037	0.057	0.517	0.054	0.043	0.211	-0.053	0.040	0.184	0.002	0.045	0.966	0.004	0.022	0.859	1.000	0.292	-0.002	0.024	0.931	1.000	0.189
28	rs1928295	-0.073	0.058	0.207	-0.071	0.044	0.102	-0.070	0.040	0.077	0.019	0.045	0.679	-0.049	0.023	0.031	1.000	0.399	-0.044	0.025	0.071	1.000	0.254
29	rs2033529	-0.032	0.084	0.704	-0.030	0.059	0.608	0.044	0.052	0.399	0.022	0.059	0.708	0.009	0.030	0.774	1.000	0.759	0.015	0.032	0.650	1.000	0.635
30	rs2033732	0.053	0.057	0.354	0.041	0.044	0.354	-0.049	0.041	0.230	0.026	0.045	0.556	0.011	0.023	0.627	1.000	0.352	0.003	0.025	0.900	1.000	0.268
31	rs205262	-0.146	0.077	0.059	0.079	0.060	0.194	-0.071	0.060	0.233	-0.101	0.065	0.118	-0.049	0.032	0.128	1.000	**0.078**	-0.029	0.036	0.422	1.000	0.086
32	rs2075650	0.015	0.107	0.885	0.042	0.078	0.586	0.013	0.071	0.854	-0.034	0.080	0.672	0.009	0.041	0.820	1.000	0.923	0.008	0.044	0.852	1.000	0.788
33	rs2080454	0.009	0.060	0.882	-0.067	0.043	0.117	0.054	0.040	0.179	-0.017	0.045	0.707	-0.005	0.023	0.840	1.000	0.222	-0.007	0.024	0.780	1.000	0.114
34	rs2112347	-0.102	0.057	0.072	-0.034	0.043	0.430	0.063	0.040	0.117	0.076	0.045	0.091	0.014	0.023	0.548	1.000	**0.031**	0.035	0.025	0.151	1.000	0.143
35	rs2176040	0.043	0.110	0.699	0.032	0.084	0.700	0.032	0.078	0.686	-0.058	0.084	0.494	0.010	0.044	0.823	1.000	0.831	0.004	0.047	0.938	1.000	0.679
36	rs2207139	0.010	0.078	0.899	-0.022	0.062	0.728	0.022	0.063	0.724	-0.021	0.065	0.749	-0.004	0.033	0.915	1.000	0.950	-0.006	0.036	0.860	1.000	0.854
37	rs2287019	0.077	0.072	0.283	0.033	0.054	0.540	-0.084	0.050	0.097	0.066	0.059	0.264	0.010	0.029	0.727	1.000	0.144	-0.003	0.031	0.932	1.000	0.112
38	rs2365389	0.065	0.081	0.427	0.130	0.062	0.035	0.008	0.063	0.894	-0.157	0.065	0.017	0.010	0.033	0.754	1.000	**0.013**	-0.001	0.037	0.989	1.000	**0.006**
39	rs2820292	-0.038	0.069	0.581	-0.061	0.056	0.274	-0.029	0.051	0.573	2.04E-04	0.055	0.997	-0.031	0.028	0.274	1.000	0.891	-0.029	0.031	0.342	1.000	0.736
40	rs2836754	0.018	0.060	0.769	-0.004	0.044	0.928	0.035	0.041	0.391	-0.028	0.047	0.545	0.006	0.023	0.801	1.000	0.769	0.004	0.025	0.881	1.000	0.580
41	rs29941	-0.017	0.073	0.812	0.112	0.051	0.028	-0.031	0.050	0.534	0.100	0.055	0.069	0.047	0.028	0.093	1.000	0.125	0.057	0.030	0.056	1.000	0.089
42	rs3101336	0.203	0.109	0.062	-0.025	0.078	0.746	-0.011	0.072	0.882	0.033	0.085	0.694	0.027	0.041	0.517	1.000	0.340	-0.003	0.045	0.945	1.000	0.871
43	rs3817334	0.011	0.063	0.866	0.025	0.047	0.593	0.013	0.045	0.771	-0.025	0.050	0.612	0.006	0.025	0.795	1.000	0.899	0.006	0.027	0.833	1.000	0.747
44	rs3849570	0.046	0.057	0.420	-0.043	0.043	0.313	-0.032	0.040	0.417	0.012	0.045	0.795	-0.012	0.022	0.588	1.000	0.552	-0.023	0.024	0.350	1.000	0.647
45	rs3888190	0.005	0.100	0.957	0.058	0.076	0.446	0.054	0.071	0.449	0.004	0.080	0.962	0.035	0.040	0.384	1.000	0.940	0.040	0.044	0.354	1.000	0.861
46	rs4256980	-0.071	0.060	0.242	0.109	0.043	0.011	-0.001	0.041	0.981	-0.033	0.045	0.470	0.012	0.023	0.595	1.000	**0.045**	0.026	0.025	0.292	1.000	**0.053**

Table 41 (continued): Association between 64 SNPs and fiber intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	0.052	0.065	0.425	-0.036	0.050	0.470	-0.009	0.046	0.836	-0.038	0.054	0.480	-0.014	0.026	0.604	1.000	0.699	-0.026	0.029	0.360	1.000	0.894
48	rs4787491	-0.018	0.058	0.759	-0.020	0.041	0.623	-0.040	0.041	0.330	0.011	0.045	0.802	-0.018	0.023	0.425	1.000	0.871	-0.018	0.024	0.462	1.000	0.701
49	rs492400	-0.121	0.073	0.095	-0.015	0.051	0.774	2.17E-04	0.048	0.996	0.091	0.053	0.085	0.003	0.027	0.912	1.000	0.120	0.023	0.029	0.427	1.000	0.299
50	rs6567160	-0.026	0.079	0.744	-0.020	0.056	0.713	-0.052	0.054	0.336	0.058	0.061	0.341	-0.012	0.030	0.697	1.000	0.588	-0.009	0.033	0.775	1.000	0.388
51	rs6804842	0.082	0.060	0.174	0.072	0.046	0.116	0.004	0.043	0.925	-0.056	0.046	0.220	0.018	0.024	0.439	1.000	0.154	0.007	0.026	0.797	1.000	0.140
52	rs7138803	0.010	0.068	0.881	0.055	0.049	0.262	-0.030	0.046	0.519	0.018	0.052	0.730	0.012	0.026	0.643	1.000	0.658	0.012	0.028	0.660	1.000	0.449
53	rs7141420	-0.030	0.057	0.604	0.043	0.043	0.309	0.033	0.040	0.414	0.008	0.044	0.852	0.020	0.022	0.378	1.000	0.745	0.029	0.024	0.239	1.000	0.838
54	rs7164727	-0.020	0.067	0.763	0.112	0.048	0.021	-0.010	0.047	0.834	0.059	0.050	0.237	0.041	0.026	0.109	1.000	0.233	0.052	0.028	0.062	1.000	0.194
55	rs7239883	0.030	0.063	0.631	-0.037	0.045	0.422	0.016	0.043	0.711	0.057	0.048	0.237	0.014	0.024	0.574	1.000	0.553	0.011	0.026	0.683	1.000	0.366
56	rs7243357	0.063	0.070	0.370	-0.035	0.051	0.489	-0.049	0.053	0.360	0.124	0.054	0.023	0.019	0.028	0.500	1.000	**0.077**	0.010	0.031	0.731	1.000	**0.041**
57	rs7599312	0.102	0.219	0.641	0.029	0.158	0.855	0.007	0.123	0.957	-0.116	0.158	0.463	-0.006	0.077	0.943	1.000	0.853	-0.021	0.083	0.800	1.000	0.775
58	rs7715256	-0.256	0.151	0.091	0.105	0.115	0.362	0.232	0.114	0.043	0.039	0.115	0.731	0.064	0.061	0.288	1.000	**0.078**	0.126	0.066	0.057	1.000	0.482
59	rs7903146	0.102	0.198	0.607	0.099	0.134	0.457	0.003	0.144	0.983	0.284	0.150	0.060	0.120	0.076	0.114	1.000	0.598	0.123	0.082	0.134	1.000	0.393
60	rs9374842	-0.144	0.107	0.178	-0.060	0.073	0.408	-0.111	0.071	0.118	-0.027	0.078	0.729	-0.079	0.040	0.046	1.000	0.782	-0.069	0.043	0.107	1.000	0.721
61	rs9400239	-0.001	0.064	0.991	-0.053	0.047	0.262	0.022	0.044	0.621	-0.013	0.051	0.804	-0.011	0.025	0.659	1.000	0.713	-0.013	0.027	0.635	1.000	0.512
62	rs9641123	0.055	0.063	0.379	-0.098	0.045	0.031	0.025	0.043	0.561	0.013	0.048	0.788	-0.008	0.024	0.728	1.000	0.126	-0.019	0.026	0.458	1.000	0.104
63	rs977747	-0.183	0.158	0.246	-0.059	0.110	0.594	-0.140	0.107	0.192	-0.079	0.101	0.436	-0.104	0.057	0.067	1.000	0.897	-0.093	0.061	0.130	1.000	0.857
64	rs9914578	0.041	0.071	0.561	-0.043	0.052	0.409	0.024	0.051	0.634	0.017	0.057	0.768	0.005	0.028	0.847	1.000	0.730	-0.001	0.031	0.966	1.000	0.608

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0.05$) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

Table 42: Association between 64 SNPs and %protein intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	0.021	0.060	0.728	0.035	0.044	0.424	-0.026	0.041	0.531	-0.091	0.047	0.053	-0.018	0.023	0.448	1.000	0.227	-0.025	0.025	0.331	1.000	0.146
2	rs1016287	-0.015	0.064	0.811	-0.019	0.048	0.692	-0.076	0.049	0.125	0.019	0.050	0.708	-0.024	0.026	0.355	1.000	0.602	-0.026	0.028	0.365	1.000	0.399
3	rs10182181	-0.005	0.058	0.934	-0.028	0.043	0.510	0.008	0.042	0.851	-0.049	0.045	0.269	-0.020	0.023	0.395	1.000	0.807	-0.022	0.025	0.373	1.000	0.638
4	rs10733682	-0.039	0.065	0.550	0.023	0.051	0.648	-0.057	0.047	0.227	0.103	0.055	0.060	0.006	0.027	0.820	1.000	0.138	0.015	0.029	0.605	1.000	**0.085**
5	rs10938397	0.018	0.065	0.781	-0.054	0.047	0.258	0.003	0.047	0.942	-0.074	0.051	0.150	-0.030	0.026	0.236	1.000	0.564	-0.039	0.028	0.158	1.000	0.503
6	rs10968576	-0.024	0.077	0.758	0.041	0.057	0.468	0.006	0.054	0.917	0.021	0.060	0.729	0.015	0.030	0.619	1.000	0.918	0.022	0.033	0.501	1.000	0.902
7	rs11030104	-0.047	0.056	0.399	-0.058	0.041	0.160	0.052	0.041	0.204	0.036	0.044	0.412	3.15E-04	0.022	0.989	1.000	0.173	0.009	0.024	0.703	1.000	0.127
8	rs11126666	-0.129	0.061	0.035	-0.005	0.046	0.912	0.135	0.046	0.003	0.006	0.049	0.904	0.019	0.025	0.454	1.000	**0.005**	0.047	0.027	0.080	1.000	**0.057**
9	rs11191560	0.050	0.066	0.444	0.031	0.048	0.520	4.18E-04	0.046	0.993	0.058	0.052	0.268	0.031	0.026	0.232	1.000	0.849	0.027	0.028	0.330	1.000	0.706
10	rs11583200	0.015	0.094	0.878	-0.120	0.077	0.122	-0.020	0.077	0.800	-0.025	0.088	0.779	-0.043	0.042	0.301	1.000	0.684	-0.057	0.046	0.219	1.000	0.597
11	rs11688816	0.009	0.063	0.891	-0.008	0.047	0.862	-0.042	0.045	0.345	-0.003	0.049	0.951	-0.015	0.025	0.554	1.000	0.898	-0.019	0.027	0.481	1.000	0.807
12	rs12286929	-0.033	0.069	0.628	0.023	0.047	0.630	0.069	0.047	0.147	0.051	0.050	0.309	0.036	0.026	0.162	1.000	0.646	0.047	0.028	0.089	1.000	0.786
13	rs12429545	0.003	0.068	0.970	-0.020	0.047	0.674	0.019	0.048	0.693	0.033	0.054	0.541	0.008	0.026	0.770	1.000	0.891	0.009	0.029	0.763	1.000	0.735
14	rs12566985	0.068	0.074	0.354	0.065	0.055	0.242	0.052	0.054	0.334	-0.055	0.060	0.360	0.032	0.030	0.280	1.000	0.417	0.025	0.032	0.440	1.000	0.280
15	rs12940622	-0.038	0.062	0.539	0.060	0.046	0.200	0.009	0.045	0.843	0.049	0.048	0.313	0.026	0.025	0.289	1.000	0.581	0.038	0.027	0.156	1.000	0.707
16	rs13021737	-0.024	0.113	0.832	0.097	0.081	0.231	0.069	0.077	0.374	0.014	0.090	0.879	0.050	0.044	0.252	1.000	0.805	0.063	0.047	0.183	1.000	0.786
17	rs13201877	-0.265	0.182	0.145	0.054	0.106	0.612	0.053	0.107	0.618	-0.121	0.117	0.300	-0.027	0.060	0.656	1.000	0.319	0.002	0.063	0.972	1.000	0.454
18	rs1441264	0.040	0.060	0.502	-0.036	0.043	0.407	0.067	0.041	0.105	0.005	0.046	0.918	0.018	0.023	0.438	1.000	0.365	0.014	0.025	0.575	1.000	0.222
19	rs1460676	-0.022	0.059	0.702	0.059	0.045	0.190	-0.070	0.042	0.092	0.041	0.046	0.371	0.001	0.023	0.964	1.000	0.138	0.005	0.025	0.831	1.000	**0.070**
20	rs1516725	-0.203	0.105	0.054	0.003	0.084	0.976	0.138	0.073	0.061	-0.021	0.085	0.805	0.008	0.042	0.848	1.000	**0.064**	0.049	0.046	0.287	1.000	0.295
21	rs1528435	0.043	0.062	0.492	0.088	0.045	0.050	-0.003	0.044	0.952	0.022	0.048	0.642	0.037	0.024	0.126	1.000	0.533	0.036	0.026	0.170	1.000	0.335
22	rs1558902	-0.025	0.082	0.761	0.025	0.063	0.693	-0.031	0.065	0.628	0.052	0.072	0.471	0.006	0.035	0.861	1.000	0.808	0.013	0.038	0.738	1.000	0.671
23	rs16851483	-0.036	0.064	0.577	0.024	0.049	0.620	-0.016	0.047	0.738	-0.007	0.052	0.900	-0.006	0.026	0.832	1.000	0.887	4.36E-04	0.029	0.988	1.000	0.830

Table 42 (continued): Association between 64 SNPs and %protein intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	-0.012	0.060	0.848	0.031	0.041	0.456	-0.061	0.042	0.151	0.097	0.045	0.032	0.015	0.023	0.521	1.000	**0.077**	0.019	0.025	0.440	1.000	**0.036**
25	rs17203016	-0.165	0.086	0.056	0.003	0.062	0.967	0.056	0.058	0.333	0.013	0.064	0.840	-0.002	0.033	0.958	1.000	0.200	0.026	0.035	0.469	1.000	0.796
26	rs17405819	-0.076	0.059	0.202	0.056	0.043	0.195	0.029	0.042	0.484	-0.089	0.045	0.050	-0.010	0.023	0.678	1.000	**0.058**	0.002	0.025	0.930	1.000	**0.050**
27	rs17724992	-0.003	0.057	0.958	0.056	0.043	0.194	-0.007	0.041	0.861	-0.090	0.045	0.047	-0.010	0.023	0.662	1.000	0.138	-0.011	0.025	0.650	1.000	**0.064**
28	rs1928295	-0.026	0.058	0.655	-0.018	0.044	0.685	-0.033	0.041	0.417	0.010	0.046	0.836	-0.017	0.023	0.456	1.000	0.916	-0.015	0.025	0.536	1.000	0.785
29	rs2033529	0.071	0.084	0.397	0.046	0.059	0.436	-0.088	0.053	0.094	0.021	0.060	0.718	-0.002	0.031	0.942	1.000	0.235	-0.013	0.033	0.683	1.000	0.185
30	rs2033732	-0.005	0.057	0.934	-0.022	0.044	0.620	0.051	0.042	0.231	-0.052	0.045	0.251	-0.005	0.023	0.822	1.000	0.398	-0.005	0.025	0.834	1.000	0.228
31	rs205262	-0.074	0.077	0.340	-0.033	0.061	0.590	-0.011	0.061	0.856	-0.037	0.065	0.576	-0.035	0.033	0.285	1.000	0.939	-0.026	0.036	0.462	1.000	0.953
32	rs2075650	-0.062	0.106	0.558	0.006	0.078	0.943	-0.048	0.072	0.507	0.096	0.080	0.234	0.002	0.041	0.965	1.000	0.530	0.013	0.044	0.770	1.000	0.410
33	rs2080454	0.111	0.060	0.065	-0.001	0.043	0.975	0.011	0.041	0.782	-0.006	0.045	0.895	0.018	0.023	0.436	1.000	0.405	0.002	0.025	0.939	1.000	0.956
34	rs2112347	0.021	0.057	0.712	-0.035	0.043	0.409	0.034	0.041	0.403	-0.009	0.045	0.834	0.002	0.023	0.947	1.000	0.669	-0.002	0.025	0.929	1.000	0.492
35	rs2176040	-0.064	0.110	0.560	-0.004	0.084	0.959	0.044	0.080	0.579	-0.037	0.085	0.660	-0.008	0.044	0.855	1.000	0.847	0.003	0.048	0.957	1.000	0.778
36	rs2207139	0.032	0.079	0.687	0.037	0.062	0.552	0.011	0.064	0.864	-0.018	0.066	0.788	0.015	0.033	0.656	1.000	0.936	0.011	0.037	0.762	1.000	0.834
37	rs2287019	-0.148	0.072	0.039	0.057	0.054	0.286	0.098	0.051	0.058	0.146	0.060	0.015	0.057	0.029	0.047	1.000	**0.012**	0.097	0.032	0.002	0.128	0.547
38	rs2365389	-0.100	0.081	0.216	-0.156	0.061	0.011	0.002	0.065	0.976	-0.023	0.066	0.724	-0.070	0.034	0.037	1.000	0.282	-0.064	0.037	0.084	1.000	0.161
39	rs2820292	0.022	0.069	0.755	-0.092	0.056	0.102	0.025	0.052	0.629	0.021	0.056	0.707	-0.007	0.029	0.806	1.000	0.377	-0.013	0.031	0.680	1.000	0.236
40	rs2836754	0.014	0.060	0.818	-0.029	0.044	0.508	-0.033	0.042	0.431	-0.030	0.047	0.527	-0.024	0.023	0.309	1.000	0.924	-0.031	0.025	0.228	1.000	0.998
41	rs29941	0.004	0.073	0.958	0.028	0.051	0.587	-0.055	0.051	0.285	0.011	0.056	0.838	-0.004	0.028	0.873	1.000	0.692	-0.006	0.030	0.845	1.000	0.486
42	rs3101336	-0.201	0.109	0.067	-0.244	0.078	0.002	-0.025	0.073	0.737	-0.066	0.085	0.442	-0.123	0.042	0.003	0.192	0.160	-0.110	0.045	0.015	1.000	0.101
43	rs3817334	9.05E-05	0.063	0.999	0.027	0.047	0.561	0.012	0.046	0.803	-0.033	0.050	0.511	0.003	0.025	0.903	1.000	0.845	0.004	0.027	0.894	1.000	0.665
44	rs3849570	0.001	0.057	0.985	0.019	0.043	0.654	-0.036	0.041	0.374	0.005	0.045	0.904	-0.004	0.023	0.847	1.000	0.808	-0.005	0.025	0.828	1.000	0.619
45	rs3888190	0.041	0.100	0.679	0.040	0.076	0.603	-0.035	0.072	0.625	-0.026	0.080	0.748	3.17E-04	0.040	0.994	1.000	0.853	-0.008	0.044	0.863	1.000	0.747
46	rs4256980	0.023	0.061	0.708	-0.009	0.043	0.828	-0.025	0.042	0.557	0.014	0.046	0.761	-0.003	0.023	0.886	1.000	0.895	-0.008	0.025	0.756	1.000	0.824

Table 42 (continued): Association between 64 SNPs and %protein intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	-0.091	0.065	0.160	-0.030	0.050	0.546	-0.003	0.047	0.946	0.033	0.054	0.537	-0.017	0.026	0.531	1.000	0.506	-0.002	0.029	0.952	1.000	0.688
48	rs4787491	0.051	0.058	0.380	-0.023	0.041	0.576	0.025	0.042	0.550	-0.057	0.045	0.209	-0.006	0.023	0.787	1.000	0.399	-0.016	0.025	0.506	1.000	0.405
49	rs492400	-0.035	0.073	0.631	-0.012	0.051	0.821	-0.040	0.049	0.422	0.057	0.054	0.292	-0.006	0.028	0.835	1.000	0.573	-0.001	0.030	0.976	1.000	0.405
50	rs6567160	0.034	0.079	0.664	-0.042	0.056	0.449	0.008	0.056	0.887	-0.004	0.062	0.943	-0.006	0.031	0.837	1.000	0.862	-0.013	0.033	0.685	1.000	0.805
51	rs6804842	0.054	0.061	0.373	0.007	0.046	0.872	0.074	0.044	0.097	-0.052	0.046	0.260	0.018	0.024	0.451	1.000	0.233	0.011	0.026	0.664	1.000	0.145
52	rs7138803	-0.077	0.067	0.254	0.012	0.049	0.801	-0.055	0.047	0.245	0.002	0.052	0.969	-0.024	0.026	0.349	1.000	0.606	-0.015	0.028	0.593	1.000	0.568
53	rs7141420	-0.008	0.057	0.890	0.029	0.043	0.489	0.005	0.041	0.908	0.022	0.044	0.625	0.014	0.023	0.530	1.000	0.949	0.018	0.025	0.457	1.000	0.914
54	rs7164727	-0.101	0.067	0.133	0.014	0.048	0.778	-0.041	0.048	0.396	-0.018	0.051	0.723	-0.028	0.026	0.283	1.000	0.565	-0.015	0.028	0.595	1.000	0.725
55	rs7239883	0.049	0.062	0.434	-0.054	0.045	0.236	0.044	0.044	0.314	-0.066	0.049	0.171	-0.011	0.024	0.647	1.000	0.195	-0.022	0.026	0.408	1.000	0.164
56	rs7243357	0.068	0.070	0.330	0.004	0.051	0.934	0.136	0.055	0.013	-0.008	0.055	0.881	0.047	0.028	0.098	1.000	0.216	0.043	0.031	0.168	1.000	0.114
57	rs7599312	0.063	0.219	0.773	0.103	0.158	0.513	-0.074	0.126	0.556	-0.355	0.159	0.026	-0.081	0.078	0.301	1.000	0.190	-0.102	0.084	0.224	1.000	0.119
58	rs7715256	-0.312	0.150	0.038	-0.075	0.115	0.514	-0.044	0.116	0.708	-0.045	0.116	0.697	-0.098	0.061	0.110	1.000	0.473	-0.055	0.067	0.413	1.000	0.977
59	rs7903146	0.009	0.198	0.963	-0.018	0.135	0.897	0.004	0.147	0.981	-0.017	0.152	0.913	-0.008	0.077	0.921	1.000	0.999	-0.011	0.083	0.899	1.000	0.993
60	rs9374842	-0.283	0.106	0.008	0.043	0.073	0.557	-0.015	0.073	0.833	0.023	0.079	0.770	-0.026	0.040	0.517	1.000	**0.067**	0.017	0.043	0.702	1.000	0.849
61	rs9400239	0.111	0.063	0.080	-0.031	0.047	0.502	-0.013	0.045	0.767	-0.028	0.051	0.582	-0.002	0.025	0.923	1.000	0.271	-0.024	0.027	0.385	1.000	0.957
62	rs9641123	0.089	0.062	0.156	0.020	0.046	0.660	-0.060	0.044	0.175	0.010	0.048	0.832	0.004	0.024	0.885	1.000	0.253	-0.012	0.026	0.655	1.000	0.390
63	rs977747	-0.120	0.158	0.447	-0.124	0.109	0.257	0.018	0.110	0.868	0.116	0.102	0.259	-0.009	0.057	0.878	1.000	0.370	0.008	0.062	0.894	1.000	0.276
64	rs9914578	0.053	0.070	0.454	-0.002	0.052	0.972	0.012	0.052	0.814	0.096	0.058	0.097	0.035	0.028	0.221	1.000	0.597	0.031	0.031	0.314	1.000	0.406

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

Table 43: Association between 64 SNPs and %fat intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	0.002	0.059	0.967	0.040	0.043	0.351	0.04	0.037	0.279	-0.004	0.042	0.933	0.023	0.022	0.283	1.000	0.825	0.027	0.023	0.255	1.000	0.686
2	rs1016287	0.006	0.063	0.919	-0.015	0.047	0.749	-0.033	0.044	0.456	0.003	0.045	0.940	-0.012	0.024	0.623	1.000	0.933	-0.015	0.026	0.565	1.000	0.846
3	rs10182181	0.114	0.057	0.046	-0.022	0.043	0.610	0.006	0.038	0.881	-0.010	0.040	0.795	0.009	0.021	0.659	1.000	0.245	-0.008	0.023	0.737	1.000	0.888
4	rs10733682	0.067	0.064	0.296	0.023	0.050	0.651	-0.056	0.043	0.185	-0.046	0.049	0.352	-0.015	0.025	0.536	1.000	0.316	-0.030	0.027	0.266	1.000	0.451
5	rs10938397	0.074	0.064	0.248	-0.037	0.047	0.424	-0.042	0.042	0.327	-0.074	0.046	0.108	-0.033	0.024	0.171	1.000	0.302	-0.051	0.026	0.051	1.000	0.826
6	rs10968576	-0.017	0.076	0.825	0.006	0.056	0.911	0.048	0.049	0.324	-0.006	0.054	0.906	0.014	0.028	0.628	1.000	0.846	0.019	0.030	0.542	1.000	0.730
7	rs11030104	-0.048	0.055	0.388	-0.079	0.041	0.051	-1.73E-04	0.037	0.996	0.032	0.040	0.425	-0.019	0.021	0.364	1.000	0.225	-0.014	0.022	0.530	1.000	0.132
8	rs11126666	-0.114	0.060	0.061	-0.043	0.045	0.337	-0.089	0.041	0.031	-0.063	0.044	0.152	-0.073	0.023	0.001	0.064	0.777	-0.067	0.025	0.008	0.512	0.749
9	rs11191560	0.072	0.065	0.269	-0.034	0.048	0.472	-0.032	0.041	0.430	-0.047	0.047	0.316	-0.022	0.024	0.352	1.000	0.475	-0.037	0.026	0.149	1.000	0.970
10	rs11583200	0.095	0.093	0.307	-0.169	0.076	0.026	-0.013	0.070	0.850	-0.141	0.078	0.074	-0.067	0.039	0.087	1.000	**0.097**	-0.101	0.043	0.018	1.000	0.266
11	rs11688816	0.036	0.062	0.565	0.046	0.047	0.322	-0.019	0.041	0.640	-0.038	0.044	0.396	-7.47E-05	0.023	0.997	1.000	0.522	-0.006	0.025	0.812	1.000	0.394
12	rs12286929	-0.108	0.067	0.109	0.033	0.047	0.477	-0.018	0.043	0.669	0.022	0.045	0.625	-0.004	0.024	0.853	1.000	0.324	0.011	0.026	0.677	1.000	0.685
13	rs12429545	0.038	0.067	0.566	-0.006	0.046	0.901	0.018	0.043	0.682	-0.053	0.049	0.277	-0.004	0.025	0.862	1.000	0.645	-0.011	0.027	0.679	1.000	0.550
14	rs12566985	-0.089	0.073	0.223	0.130	0.054	0.017	0.067	0.049	0.166	-0.071	0.054	0.186	0.024	0.028	0.388	1.000	**0.017**	0.043	0.030	0.150	1.000	**0.025**
15	rs12940622	-0.069	0.061	0.259	0.037	0.046	0.420	0.054	0.040	0.179	0.001	0.043	0.989	0.017	0.023	0.451	1.000	0.367	0.032	0.025	0.203	1.000	0.658
16	rs13021737	0.028	0.111	0.798	0.105	0.079	0.183	0.025	0.070	0.721	0.099	0.081	0.220	0.066	0.041	0.107	1.000	0.834	0.072	0.044	0.102	1.000	0.692
17	rs13201877	-0.246	0.179	0.171	0.056	0.104	0.592	0.021	0.097	0.824	-0.097	0.105	0.355	-0.028	0.056	0.614	1.000	0.420	-0.005	0.059	0.934	1.000	0.552
18	rs1441264	6.53E-05	0.059	0.999	-0.060	0.043	0.157	0.029	0.037	0.442	-0.048	0.041	0.237	-0.019	0.022	0.371	1.000	0.362	-0.022	0.023	0.337	1.000	0.215
19	rs1460676	0.029	0.058	0.620	0.076	0.044	0.085	0.026	0.038	0.488	0.033	0.041	0.421	0.041	0.022	0.062	1.000	0.837	0.043	0.024	0.070	1.000	0.669
20	rs1516725	-0.097	0.103	0.347	-0.014	0.082	0.866	0.030	0.066	0.647	-0.066	0.076	0.387	-0.024	0.039	0.537	1.000	0.684	-0.012	0.043	0.780	1.000	0.635
21	rs1528435	0.109	0.062	0.078	0.058	0.044	0.189	-0.013	0.040	0.751	0.026	0.043	0.542	0.033	0.023	0.143	1.000	0.365	0.021	0.024	0.379	1.000	0.490
22	rs1558902	-0.001	0.081	0.992	0.094	0.062	0.129	-0.035	0.058	0.547	0.034	0.065	0.601	0.023	0.033	0.474	1.000	0.488	0.028	0.036	0.431	1.000	0.313
23	rs16851483	-0.018	0.064	0.774	0.072	0.048	0.140	-0.003	0.042	0.946	0.051	0.047	0.278	0.028	0.024	0.248	1.000	0.551	0.036	0.026	0.170	1.000	0.477

Table 43 (continued): Association between 64 SNPs and %fat intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	-0.038	0.059	0.522	-0.008	0.041	0.851	0.033	0.038	0.392	0.003	0.041	0.942	0.004	0.021	0.849	1.000	0.766	0.010	0.023	0.651	1.000	0.753
25	rs17203016	-0.093	0.085	0.277	-0.023	0.061	0.707	0.010	0.052	0.846	-0.066	0.058	0.250	-0.033	0.030	0.284	1.000	0.673	-0.024	0.033	0.465	1.000	0.616
26	rs17405819	-0.065	0.058	0.267	-0.023	0.042	0.594	0.053	0.037	0.155	-0.007	0.041	0.858	0.001	0.021	0.965	1.000	0.311	0.011	0.023	0.626	1.000	0.348
27	rs17724992	-0.009	0.056	0.871	0.028	0.043	0.514	0.023	0.037	0.523	-0.020	0.041	0.626	0.008	0.021	0.703	1.000	0.812	0.011	0.023	0.633	1.000	0.655
28	rs1928295	1.71E-04	0.057	0.998	-0.042	0.043	0.327	0.032	0.037	0.389	0.074	0.041	0.074	0.020	0.021	0.346	1.000	0.259	0.023	0.023	0.310	1.000	0.144
29	rs2033529	0.076	0.083	0.362	0.062	0.058	0.282	-0.142	0.047	0.003	0.048	0.053	0.365	-0.013	0.028	0.637	1.000	**0.009**	-0.025	0.030	0.404	1.000	**0.006**
30	rs2033732	0.028	0.056	0.621	-0.002	0.044	0.962	0.041	0.038	0.278	-0.058	0.040	0.149	1.93E-04	0.022	0.993	1.000	0.320	-0.005	0.023	0.845	1.000	0.200
31	rs205262	-0.026	0.076	0.733	-0.050	0.060	0.400	0.030	0.055	0.591	-0.098	0.059	0.096	-0.035	0.031	0.254	1.000	0.459	-0.036	0.033	0.274	1.000	0.276
32	rs2075650	-0.238	0.104	0.023	-0.098	0.077	0.201	0.015	0.065	0.813	0.071	0.072	0.328	-0.031	0.038	0.416	1.000	**0.066**	0.001	0.041	0.984	1.000	0.266
33	rs2080454	0.059	0.059	0.321	0.029	0.042	0.487	-0.044	0.037	0.234	0.027	0.041	0.508	0.008	0.021	0.713	1.000	0.364	2.46E-04	0.023	0.991	1.000	0.311
34	rs2112347	0.015	0.056	0.792	-0.002	0.042	0.962	-0.023	0.037	0.542	0.015	0.041	0.707	-0.002	0.021	0.940	1.000	0.901	-0.004	0.023	0.850	1.000	0.787
35	rs2176040	0.053	0.109	0.629	0.037	0.082	0.656	0.092	0.072	0.201	-0.014	0.076	0.855	0.042	0.041	0.302	1.000	0.792	0.041	0.044	0.359	1.000	0.599
36	rs2207139	0.017	0.077	0.822	0.027	0.061	0.660	0.035	0.058	0.544	-0.036	0.059	0.543	0.010	0.031	0.746	1.000	0.831	0.009	0.034	0.799	1.000	0.648
37	rs2287019	-0.013	0.071	0.857	0.043	0.053	0.418	0.052	0.047	0.261	0.013	0.054	0.812	0.030	0.027	0.263	1.000	0.860	0.038	0.029	0.199	1.000	0.851
38	rs2365389	0.108	0.080	0.180	-0.051	0.060	0.394	-0.001	0.059	0.984	-0.001	0.060	0.982	0.002	0.032	0.952	1.000	0.470	-0.018	0.034	0.610	1.000	0.791
39	rs2820292	0.010	0.068	0.887	-0.083	0.055	0.129	0.011	0.047	0.812	-0.044	0.050	0.373	-0.027	0.027	0.306	1.000	0.546	-0.034	0.029	0.241	1.000	0.410
40	rs2836754	-0.013	0.059	0.826	-0.062	0.043	0.152	0.030	0.038	0.423	0.045	0.042	0.292	0.004	0.022	0.843	1.000	0.282	0.007	0.024	0.763	1.000	0.156
41	rs29941	0.051	0.072	0.483	-0.016	0.050	0.752	-0.039	0.046	0.400	0.057	0.050	0.256	0.006	0.026	0.831	1.000	0.466	-0.001	0.028	0.963	1.000	0.350
42	rs3101336	-0.081	0.107	0.450	-0.074	0.077	0.338	-0.029	0.066	0.665	-0.047	0.077	0.545	-0.052	0.039	0.185	1.000	0.963	-0.047	0.042	0.259	1.000	0.904
43	rs3817334	-0.053	0.062	0.393	-0.004	0.046	0.925	0.046	0.042	0.272	-0.005	0.045	0.914	0.004	0.024	0.849	1.000	0.589	0.014	0.025	0.577	1.000	0.632
44	rs3849570	0.027	0.056	0.628	0.049	0.042	0.247	-0.018	0.037	0.631	-0.023	0.041	0.580	0.004	0.021	0.842	1.000	0.557	3.92E-04	0.023	0.986	1.000	0.391
45	rs3888190	-0.085	0.099	0.388	-0.025	0.075	0.736	-0.023	0.065	0.726	0.015	0.072	0.834	-0.022	0.038	0.554	1.000	0.879	-0.012	0.041	0.776	1.000	0.905
46	rs4256980	0.068	0.060	0.254	0.024	0.042	0.564	-0.006	0.038	0.868	-0.001	0.041	0.980	0.013	0.022	0.549	1.000	0.728	0.005	0.023	0.842	1.000	0.851

Table 43 (continued): Association between 64 SNPs and %fat intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	-0.138	0.064	0.031	-0.054	0.049	0.271	0.007	0.042	0.865	0.044	0.049	0.365	-0.020	0.025	0.408	1.000	0.108	2.87E-04	0.027	0.991	1.000	0.357
48	rs4787491	0.031	0.058	0.592	0.024	0.041	0.560	0.013	0.038	0.738	-0.056	0.041	0.168	-0.001	0.021	0.976	1.000	0.450	-0.006	0.023	0.806	1.000	0.317
49	rs492400	-0.009	0.072	0.902	-0.067	0.051	0.187	0.012	0.045	0.787	-0.007	0.048	0.884	-0.016	0.026	0.525	1.000	0.694	-0.017	0.027	0.526	1.000	0.487
50	rs6567160	0.059	0.078	0.451	0.027	0.055	0.618	0.096	0.050	0.057	0.023	0.055	0.678	0.053	0.029	0.066	1.000	0.743	0.052	0.031	0.093	1.000	0.540
51	rs6804842	0.029	0.060	0.630	0.011	0.045	0.803	0.032	0.040	0.423	-0.088	0.042	0.033	-0.009	0.022	0.692	1.000	0.150	-0.015	0.024	0.534	1.000	**0.088**
52	rs7138803	-0.098	0.066	0.142	0.066	0.048	0.169	-1.07E-04	0.042	0.998	-0.039	0.047	0.401	-0.007	0.024	0.783	1.000	0.196	0.008	0.026	0.775	1.000	0.284
53	rs7141420	0.007	0.056	0.898	0.031	0.042	0.465	0.020	0.037	0.595	0.032	0.039	0.415	0.024	0.021	0.249	1.000	0.983	0.027	0.023	0.234	1.000	0.970
54	rs7164727	-0.079	0.066	0.234	4.24E-04	0.047	0.993	-0.006	0.043	0.890	0.074	0.045	0.103	0.009	0.024	0.717	1.000	0.264	0.022	0.026	0.390	1.000	0.377
55	rs7239883	-0.009	0.062	0.880	-0.009	0.045	0.834	0.008	0.040	0.846	-0.017	0.044	0.697	-0.006	0.023	0.800	1.000	0.979	-0.005	0.025	0.832	1.000	0.910
56	rs7243357	0.081	0.069	0.240	-0.025	0.050	0.621	0.016	0.050	0.741	0.019	0.049	0.697	0.015	0.027	0.562	1.000	0.671	0.004	0.029	0.892	1.000	0.784
57	rs7599312	0.072	0.216	0.739	0.013	0.155	0.935	0.034	0.114	0.764	-0.069	0.143	0.631	0.007	0.073	0.922	1.000	0.934	-0.001	0.077	0.988	1.000	0.849
58	rs7715256	-0.250	0.148	0.093	-0.005	0.113	0.966	-0.114	0.105	0.277	0.006	0.104	0.953	-0.070	0.057	0.220	1.000	0.472	-0.039	0.062	0.529	1.000	0.672
59	rs7903146	0.194	0.195	0.320	-0.180	0.131	0.171	-0.234	0.133	0.077	-0.186	0.137	0.174	-0.147	0.072	0.040	1.000	0.303	-0.200	0.077	0.009	0.576	0.951
60	rs9374842	-0.234	0.105	0.026	0.054	0.072	0.448	-0.051	0.066	0.439	-0.002	0.071	0.976	-0.032	0.037	0.393	1.000	0.144	-0.003	0.040	0.948	1.000	0.556
61	rs9400239	0.134	0.063	0.032	-0.039	0.046	0.397	-0.027	0.041	0.507	-0.008	0.046	0.868	-0.002	0.024	0.926	1.000	0.122	-0.025	0.025	0.330	1.000	0.888
62	rs9641123	0.028	0.062	0.652	0.007	0.045	0.869	0.031	0.040	0.436	-0.050	0.043	0.248	0.002	0.023	0.927	1.000	0.539	-0.002	0.024	0.935	1.000	0.375
63	rs977747	-0.164	0.155	0.291	-0.181	0.107	0.091	-0.094	0.099	0.342	-0.004	0.092	0.964	-0.094	0.054	0.080	1.000	0.611	-0.084	0.057	0.140	1.000	0.453
64	rs9914578	0.087	0.070	0.210	-0.015	0.051	0.766	0.005	0.047	0.918	-0.010	0.052	0.844	0.008	0.027	0.778	1.000	0.652	-0.006	0.029	0.830	1.000	0.955

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

6.3.6.6 %Fat

After meta-analysis, nominal significance were found between rs11126666 on *KCNK3* (β=-0.073, SE=0.023, P=0.001) and rs7903146 on *TCF7L2* (β=-0.147, SE=0.072, P=0.040) and intake of %fat (Table 43). BMI risk allele A of rs11126666 and C of rs7903146 were all negatively associated with the outcome.

6.3.6.7 %SFA

After meta-analysis, nominal association were observed between rs1000940 on *RABEP1* (β=0.051, SE=0.022, P=0.020), rs11126666 on *KCNK3* (β=-0.051, SE=0.023, P=0.028) and rs977747 on *TAL1* (β=-0.120, SE=0.054, P=0.025) were found to be associated with %SFA intake (Table 44). BMI risk allele G of rs1000940 was positively associated while A of rs11126666 and T of rs977747 were negatively associated with %SFA intake.

6.3.6.8 %MFA

After meta-analysis, rs11126666 on *KCNK3* (β=-0.055, SE=0.024, P=0.020), rs11583200 on *ELAVL4* (β=-0.088, SE=0.040, P=0.029), rs1460676 on *FIGN* (β=0.052, SE=0.023, P=0.020), rs2176040 on *LOC646736* (β=0.091, SE=0.042, P=0.032) and rs6567160 on *MC4R* (β=0.069, SE=0.029, P=0.019) were found to be associated with %MFA intake (Table 45). BMI risk allele A of rs11126666 and C of rs11583200 would reduce while C of rs1460676, A of rs2176040 and C of rs6567160 would increase %MFA intake.

Table 44: Association between 64 SNPs and %SFA intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	0.018	0.059	0.765	0.021	0.043	0.621	0.055	0.038	0.147	0.090	0.042	0.031	0.051	0.022	0.020	1.000	0.643	0.056	0.024	0.017	1.000	0.521
2	rs1016287	0.025	0.063	0.695	-0.044	0.047	0.355	-0.007	0.045	0.875	-0.036	0.045	0.424	-0.021	0.024	0.398	1.000	0.810	-0.028	0.026	0.281	1.000	0.835
3	rs10182181	0.092	0.058	0.111	-0.036	0.043	0.409	-3.86E-04	0.038	0.992	-0.004	0.040	0.911	0.003	0.022	0.906	1.000	0.357	-0.012	0.023	0.604	1.000	0.808
4	rs10733682	0.049	0.065	0.446	0.047	0.050	0.351	-0.006	0.043	0.896	-0.040	0.049	0.415	0.007	0.025	0.789	1.000	0.560	-0.001	0.027	0.976	1.000	0.460
5	rs10938397	0.039	0.064	0.546	-0.019	0.047	0.684	-0.031	0.043	0.468	0.027	0.046	0.555	-0.002	0.024	0.936	1.000	0.706	-0.009	0.026	0.739	1.000	0.628
6	rs10968576	0.018	0.076	0.813	0.005	0.056	0.926	0.052	0.049	0.294	-0.001	0.054	0.991	0.021	0.028	0.465	1.000	0.889	0.021	0.030	0.488	1.000	0.729
7	rs11030104	-0.040	0.055	0.473	-0.014	0.041	0.728	0.027	0.037	0.463	0.002	0.039	0.963	-2.50E-04	0.021	0.990	1.000	0.759	0.006	0.023	0.780	1.000	0.747
8	rs11126666	-0.093	0.061	0.125	0.032	0.045	0.474	-0.102	0.042	0.015	-0.051	0.044	0.243	-0.051	0.023	0.028	1.000	0.146	-0.044	0.025	0.082	1.000	**0.090**
9	rs11191560	0.017	0.065	0.792	-0.023	0.048	0.630	-0.036	0.042	0.390	-0.074	0.047	0.113	-0.035	0.024	0.142	1.000	0.705	-0.044	0.026	0.092	1.000	0.724
10	rs11583200	-1.95E-05	0.093	1.000	-0.151	0.076	0.048	0.010	0.070	0.892	-0.071	0.078	0.365	-0.055	0.039	0.163	1.000	0.420	-0.066	0.043	0.125	1.000	0.300
11	rs11688816	0.004	0.062	0.953	0.036	0.047	0.443	-0.037	0.041	0.371	0.014	0.044	0.751	0.001	0.023	0.950	1.000	0.684	0.001	0.025	0.965	1.000	0.475
12	rs12286929	-0.066	0.068	0.329	0.065	0.047	0.166	-0.030	0.043	0.490	-0.009	0.045	0.849	-0.003	0.024	0.902	1.000	0.338	0.006	0.026	0.809	1.000	0.306
13	rs12429545	0.039	0.067	0.558	-0.026	0.046	0.572	0.008	0.044	0.850	-0.106	0.048	0.028	-0.027	0.025	0.269	1.000	0.230	-0.038	0.027	0.155	1.000	0.205
14	rs12566985	0.017	0.073	0.817	0.074	0.054	0.175	0.027	0.049	0.585	-0.082	0.053	0.123	0.008	0.028	0.775	1.000	0.213	0.006	0.030	0.831	1.000	0.106
15	rs12940622	-0.055	0.061	0.374	-0.011	0.046	0.810	0.015	0.041	0.703	0.028	0.043	0.513	0.003	0.023	0.911	1.000	0.703	0.012	0.025	0.631	1.000	0.819
16	rs13021737	-0.070	0.112	0.534	0.073	0.079	0.356	0.076	0.071	0.286	0.087	0.081	0.283	0.058	0.041	0.157	1.000	0.675	0.078	0.044	0.077	1.000	0.992
17	rs13201877	-0.141	0.180	0.434	0.122	0.105	0.243	0.064	0.097	0.512	-0.103	0.105	0.327	0.013	0.056	0.813	1.000	0.346	0.030	0.059	0.614	1.000	0.286
18	rs1441264	-5.87E-05	0.059	0.999	-0.046	0.043	0.284	0.019	0.038	0.609	-0.004	0.041	0.926	-0.006	0.022	0.765	1.000	0.722	-0.007	0.023	0.749	1.000	0.518
19	rs1460676	0.027	0.059	0.651	0.059	0.044	0.180	0.031	0.038	0.410	-0.034	0.041	0.408	0.019	0.022	0.382	1.000	0.456	0.018	0.024	0.447	1.000	0.274
20	rs1516725	-0.097	0.104	0.349	0.015	0.083	0.856	0.033	0.067	0.626	-0.007	0.076	0.930	-0.001	0.040	0.979	1.000	0.764	0.015	0.043	0.721	1.000	0.927
21	rs1528435	0.108	0.062	0.082	0.085	0.044	0.054	-0.013	0.040	0.753	0.008	0.043	0.844	0.035	0.023	0.120	1.000	0.214	0.024	0.024	0.325	1.000	0.237
22	rs1558902	0.004	0.081	0.960	0.094	0.062	0.134	-0.021	0.059	0.726	0.032	0.065	0.624	0.028	0.033	0.390	1.000	0.598	0.033	0.036	0.359	1.000	0.412
23	rs16851483	-0.026	0.064	0.682	0.048	0.049	0.323	-0.088	0.043	0.038	0.045	0.047	0.333	-0.008	0.024	0.730	1.000	**0.099**	-0.005	0.026	0.839	1.000	**0.045**

Table 44 (continued): Association between 64 SNPs and %SFA intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	-0.045	0.059	0.449	0.001	0.041	0.985	0.040	0.038	0.302	-0.013	0.041	0.750	0.003	0.021	0.884	1.000	0.633	0.010	0.023	0.652	1.000	0.618
25	rs17203016	0.014	0.086	0.872	-0.081	0.061	0.184	0.061	0.053	0.246	0.039	0.057	0.492	0.013	0.031	0.667	1.000	0.330	0.013	0.033	0.690	1.000	0.180
26	rs17405819	-0.060	0.059	0.310	-0.047	0.043	0.274	0.036	0.038	0.347	-0.022	0.040	0.585	-0.015	0.022	0.496	1.000	0.399	-0.008	0.023	0.741	1.000	0.322
27	rs17724992	-0.007	0.056	0.895	-0.002	0.043	0.955	0.013	0.037	0.731	0.025	0.040	0.531	0.010	0.021	0.653	1.000	0.954	0.012	0.023	0.590	1.000	0.895
28	rs1928295	-3.57E-04	0.058	0.995	0.004	0.043	0.928	0.054	0.037	0.147	0.035	0.041	0.397	0.029	0.021	0.183	1.000	0.786	0.033	0.023	0.151	1.000	0.680
29	rs2033529	0.086	0.083	0.300	0.038	0.058	0.508	-0.075	0.048	0.119	0.030	0.053	0.570	0.002	0.029	0.952	1.000	0.235	-0.010	0.030	0.753	1.000	0.213
30	rs2033732	0.001	0.057	0.983	0.004	0.044	0.921	0.075	0.038	0.051	-0.067	0.040	0.095	0.006	0.022	0.796	1.000	**0.087**	0.006	0.023	0.787	1.000	**0.038**
31	rs205262	-0.011	0.077	0.884	-0.066	0.060	0.269	0.046	0.056	0.410	-0.027	0.058	0.648	-0.013	0.031	0.680	1.000	0.580	-0.013	0.033	0.699	1.000	0.375
32	rs2075650	-0.123	0.105	0.243	-0.151	0.077	0.051	-0.018	0.066	0.780	0.098	0.072	0.171	-0.032	0.038	0.406	1.000	**0.091**	-0.018	0.041	0.664	1.000	**0.061**
33	rs2080454	0.041	0.059	0.493	0.020	0.042	0.638	-0.094	0.037	0.012	0.009	0.040	0.827	-0.018	0.021	0.391	1.000	**0.094**	-0.027	0.023	0.237	1.000	**0.073**
34	rs2112347	0.086	0.056	0.127	0.005	0.042	0.911	-0.023	0.038	0.546	0.026	0.040	0.518	0.014	0.021	0.525	1.000	0.436	0.001	0.023	0.953	1.000	0.673
35	rs2176040	-0.025	0.109	0.820	0.031	0.083	0.707	0.099	0.073	0.176	0.068	0.076	0.371	0.055	0.041	0.177	1.000	0.799	0.069	0.044	0.121	1.000	0.828
36	rs2207139	-0.071	0.078	0.357	-0.053	0.061	0.389	-0.017	0.058	0.767	0.003	0.059	0.965	-0.030	0.031	0.342	1.000	0.855	-0.022	0.034	0.528	1.000	0.806
37	rs2287019	-0.001	0.071	0.991	0.041	0.053	0.441	0.036	0.047	0.446	-0.107	0.053	0.045	-0.005	0.027	0.853	1.000	0.161	-0.006	0.029	0.845	1.000	**0.076**
38	rs2365389	0.049	0.081	0.541	-0.017	0.061	0.778	-0.016	0.059	0.791	0.026	0.059	0.661	0.006	0.032	0.853	1.000	0.877	-0.002	0.034	0.952	1.000	0.844
39	rs2820292	0.010	0.069	0.880	0.011	0.055	0.843	-0.012	0.047	0.796	-0.023	0.050	0.650	-0.006	0.027	0.813	1.000	0.964	-0.009	0.029	0.749	1.000	0.900
40	rs2836754	-0.013	0.059	0.826	-0.052	0.043	0.233	0.016	0.038	0.684	0.022	0.042	0.597	-0.004	0.022	0.859	1.000	0.596	-0.002	0.024	0.918	1.000	0.394
41	rs29941	0.008	0.072	0.915	-0.033	0.051	0.518	0.020	0.047	0.674	0.051	0.050	0.306	0.013	0.026	0.631	1.000	0.699	0.013	0.028	0.635	1.000	0.492
42	rs3101336	-0.028	0.108	0.795	0.011	0.077	0.884	-0.091	0.067	0.174	-0.010	0.076	0.896	-0.035	0.039	0.374	1.000	0.760	-0.036	0.042	0.394	1.000	0.559
43	rs3817334	-0.052	0.062	0.406	-0.037	0.046	0.425	0.055	0.042	0.188	-0.003	0.045	0.943	-0.001	0.024	0.980	1.000	0.381	0.008	0.026	0.753	1.000	0.320
44	rs3849570	0.086	0.056	0.126	0.036	0.042	0.393	-2.01E-04	0.037	0.996	0.010	0.041	0.810	0.024	0.021	0.257	1.000	0.605	0.014	0.023	0.550	1.000	0.806
45	rs3888190	-0.042	0.099	0.668	-0.029	0.075	0.703	-0.052	0.066	0.429	0.010	0.072	0.894	-0.028	0.038	0.460	1.000	0.934	-0.025	0.041	0.534	1.000	0.817
46	rs4256980	0.132	0.060	0.028	0.004	0.043	0.926	-0.008	0.038	0.839	-0.008	0.041	0.839	0.014	0.022	0.532	1.000	0.206	-0.004	0.023	0.850	1.000	0.973

Table 44 (continued): Association between 64 SNPs and %SFA intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	-0.124	0.064	0.054	-0.055	0.049	0.262	0.031	0.042	0.468	0.068	0.048	0.162	-0.004	0.025	0.869	1.000	**0.059**	0.017	0.027	0.531	1.000	0.187
48	rs4787491	0.013	0.058	0.816	0.026	0.041	0.525	-0.023	0.038	0.542	-0.078	0.040	0.052	-0.020	0.021	0.342	1.000	0.295	-0.026	0.023	0.265	1.000	0.191
49	rs492400	0.071	0.072	0.323	-0.048	0.051	0.343	0.032	0.045	0.473	0.058	0.048	0.220	0.024	0.026	0.345	1.000	0.390	0.017	0.027	0.527	1.000	0.283
50	rs6567160	-0.041	0.078	0.604	0.018	0.055	0.747	0.077	0.051	0.131	0.020	0.055	0.723	0.029	0.029	0.310	1.000	0.626	0.040	0.031	0.194	1.000	0.662
51	rs6804842	0.001	0.060	0.989	-0.003	0.045	0.955	-0.041	0.040	0.314	-0.014	0.041	0.738	-0.017	0.023	0.444	1.000	0.910	-0.020	0.024	0.405	1.000	0.805
52	rs7138803	-0.017	0.067	0.801	0.031	0.048	0.519	0.006	0.043	0.892	-0.044	0.047	0.345	-0.004	0.025	0.858	1.000	0.716	-0.002	0.026	0.926	1.000	0.517
53	rs7141420	0.045	0.057	0.427	0.065	0.042	0.119	0.064	0.038	0.088	-0.011	0.039	0.781	0.040	0.021	0.058	1.000	0.482	0.039	0.023	0.085	1.000	0.293
54	rs7164727	-0.007	0.067	0.912	-0.069	0.047	0.144	-0.008	0.044	0.862	0.086	0.045	0.057	0.003	0.024	0.888	1.000	0.122	0.005	0.026	0.846	1.000	**0.056**
55	rs7239883	0.045	0.062	0.464	-0.023	0.045	0.606	0.005	0.040	0.908	-0.016	0.043	0.709	-0.003	0.023	0.903	1.000	0.816	-0.010	0.025	0.673	1.000	0.887
56	rs7243357	0.129	0.069	0.061	-0.024	0.051	0.639	0.054	0.050	0.279	0.013	0.049	0.787	0.032	0.027	0.229	1.000	0.314	0.015	0.029	0.606	1.000	0.549
57	rs7599312	-0.105	0.217	0.627	-0.123	0.156	0.431	-0.019	0.115	0.868	-0.036	0.143	0.801	-0.056	0.073	0.442	1.000	0.949	-0.050	0.078	0.521	1.000	0.861
58	rs7715256	-0.248	0.149	0.097	0.052	0.114	0.647	-0.098	0.106	0.353	-0.091	0.103	0.378	-0.080	0.057	0.162	1.000	0.447	-0.051	0.062	0.409	1.000	0.557
59	rs7903146	0.312	0.195	0.111	-0.074	0.132	0.574	0.002	0.134	0.988	-0.238	0.136	0.080	-0.046	0.072	0.525	1.000	0.137	-0.102	0.077	0.188	1.000	0.439
60	rs9374842	-0.136	0.106	0.198	0.089	0.072	0.215	-0.038	0.066	0.569	-0.024	0.071	0.732	-0.012	0.037	0.755	1.000	0.315	0.006	0.040	0.877	1.000	0.376
61	rs9400239	0.156	0.063	0.013	-0.028	0.046	0.545	-0.012	0.041	0.769	-0.005	0.046	0.906	0.009	0.024	0.690	1.000	**0.089**	-0.015	0.025	0.560	1.000	0.938
62	rs9641123	-0.073	0.062	0.241	-0.004	0.045	0.922	-0.015	0.040	0.706	-0.038	0.043	0.372	-0.027	0.023	0.242	1.000	0.811	-0.019	0.025	0.427	1.000	0.853
63	rs977747	-0.208	0.156	0.182	-0.193	0.108	0.073	-0.019	0.100	0.851	-0.122	0.091	0.183	-0.120	0.054	0.025	1.000	0.614	-0.108	0.057	0.058	1.000	0.487
64	rs9914578	0.055	0.070	0.433	-0.050	0.051	0.332	0.004	0.048	0.940	-0.053	0.052	0.301	-0.019	0.027	0.484	1.000	0.543	-0.031	0.029	0.280	1.000	0.654

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

Table 45: Association between 64 SNPs and %MFA intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	0.018	0.059	0.755	0.029	0.043	0.503	0.041	0.039	0.296	-0.009	0.044	0.838	0.022	0.023	0.337	1.000	0.859	0.022	0.024	0.362	1.000	0.686
2	rs1016287	0.017	0.063	0.789	-0.030	0.047	0.520	-0.068	0.047	0.145	0.057	0.047	0.229	-0.009	0.025	0.705	1.000	0.271	-0.014	0.027	0.597	1.000	0.156
3	rs10182181	0.082	0.057	0.153	-0.036	0.043	0.404	0.050	0.040	0.213	-0.041	0.042	0.334	0.007	0.022	0.759	1.000	0.162	-0.007	0.024	0.787	1.000	0.211
4	rs10733682	0.073	0.065	0.261	0.009	0.050	0.865	-0.076	0.045	0.090	-0.012	0.052	0.826	-0.014	0.026	0.583	1.000	0.270	-0.031	0.028	0.276	1.000	0.413
5	rs10938397	0.081	0.064	0.205	-0.042	0.047	0.374	-0.063	0.045	0.160	-0.051	0.049	0.300	-0.032	0.025	0.198	1.000	0.285	-0.052	0.027	0.053	1.000	0.948
6	rs10968576	-0.035	0.076	0.647	0.012	0.056	0.833	0.006	0.051	0.907	-0.052	0.057	0.362	-0.014	0.029	0.641	1.000	0.830	-0.010	0.031	0.752	1.000	0.673
7	rs11030104	-0.035	0.055	0.528	-0.081	0.041	0.046	0.014	0.039	0.712	0.056	0.042	0.183	-0.009	0.021	0.682	1.000	0.105	-0.004	0.023	0.859	1.000	**0.053**
8	rs11126666	-0.067	0.061	0.271	-0.044	0.045	0.326	-0.078	0.044	0.075	-0.035	0.046	0.450	-0.055	0.024	0.020	1.000	0.908	-0.053	0.026	0.040	1.000	0.776
9	rs11191560	0.099	0.065	0.129	-0.032	0.048	0.499	-0.056	0.043	0.197	-0.047	0.049	0.340	-0.025	0.025	0.322	1.000	0.225	-0.046	0.027	0.089	1.000	0.935
10	rs11583200	0.083	0.093	0.371	-0.169	0.076	0.027	-0.062	0.073	0.395	-0.159	0.083	0.056	-0.088	0.040	0.029	1.000	0.146	-0.127	0.045	0.004	0.256	0.541
11	rs11688816	-0.003	0.062	0.958	0.061	0.047	0.194	0.007	0.043	0.879	-0.058	0.047	0.216	0.002	0.024	0.921	1.000	0.356	0.003	0.026	0.897	1.000	0.199
12	rs12286929	-0.127	0.067	0.060	0.035	0.047	0.450	-0.009	0.045	0.835	0.020	0.047	0.667	-0.004	0.025	0.857	1.000	0.230	0.015	0.027	0.580	1.000	0.781
13	rs12429545	0.038	0.067	0.576	-0.025	0.047	0.587	0.036	0.046	0.427	-0.017	0.051	0.745	0.005	0.025	0.844	1.000	0.727	-4.78E-04	0.028	0.986	1.000	0.596
14	rs12566985	-0.106	0.072	0.146	0.091	0.054	0.093	0.048	0.051	0.347	-0.043	0.057	0.451	0.013	0.029	0.651	1.000	0.102	0.035	0.031	0.263	1.000	0.220
15	rs12940622	-0.046	0.061	0.456	0.018	0.046	0.695	0.047	0.042	0.264	0.019	0.046	0.675	0.018	0.024	0.449	1.000	0.668	0.029	0.026	0.256	1.000	0.865
16	rs13021737	0.107	0.111	0.337	0.106	0.079	0.182	-0.023	0.073	0.757	-0.019	0.085	0.825	0.033	0.042	0.431	1.000	0.526	0.021	0.045	0.647	1.000	0.423
17	rs13201877	-0.211	0.180	0.240	0.072	0.104	0.494	0.049	0.101	0.632	-0.043	0.111	0.698	0.004	0.058	0.942	1.000	0.527	0.029	0.061	0.635	1.000	0.732
18	rs1441264	-0.008	0.059	0.898	-0.034	0.043	0.430	-0.013	0.039	0.738	-0.057	0.043	0.189	-0.030	0.022	0.185	1.000	0.869	-0.033	0.024	0.168	1.000	0.756
19	rs1460676	0.040	0.059	0.501	0.084	0.044	0.055	0.057	0.040	0.152	0.023	0.044	0.601	0.052	0.023	0.020	1.000	0.792	0.055	0.024	0.025	1.000	0.613
20	rs1516725	-0.133	0.103	0.200	-0.054	0.082	0.511	0.021	0.070	0.768	-0.128	0.080	0.112	-0.060	0.041	0.142	1.000	0.468	-0.047	0.044	0.294	1.000	0.376
21	rs1528435	0.111	0.062	0.073	0.039	0.044	0.381	0.012	0.042	0.768	0.036	0.045	0.427	0.040	0.023	0.086	1.000	0.622	0.028	0.025	0.261	1.000	0.893
22	rs1558902	-0.002	0.081	0.981	0.089	0.062	0.154	-0.040	0.061	0.518	0.041	0.069	0.546	0.023	0.034	0.484	1.000	0.507	0.029	0.037	0.436	1.000	0.331
23	rs16851483	-0.015	0.064	0.817	0.057	0.049	0.242	0.004	0.045	0.927	-0.016	0.050	0.751	0.010	0.025	0.686	1.000	0.713	0.015	0.027	0.589	1.000	0.552

Table 45 (continued): Association between 64 SNPs and %MFA intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	-0.040	0.059	0.499	0.004	0.041	0.919	0.025	0.040	0.526	0.038	0.043	0.378	0.013	0.022	0.544	1.000	0.734	0.022	0.024	0.355	1.000	0.845
25	rs17203016	-0.108	0.085	0.207	-0.037	0.061	0.547	0.022	0.055	0.691	-0.067	0.061	0.272	-0.035	0.031	0.264	1.000	0.557	-0.024	0.034	0.483	1.000	0.538
26	rs17405819	-0.075	0.058	0.194	-0.035	0.043	0.413	0.023	0.039	0.564	-0.001	0.043	0.981	-0.014	0.022	0.541	1.000	0.509	-0.003	0.024	0.901	1.000	0.610
27	rs17724992	-0.017	0.056	0.767	0.015	0.043	0.719	0.025	0.039	0.523	0.015	0.043	0.731	0.013	0.022	0.544	1.000	0.946	0.019	0.024	0.432	1.000	0.981
28	rs1928295	0.026	0.057	0.654	-0.013	0.043	0.754	0.036	0.039	0.357	0.044	0.044	0.315	0.023	0.022	0.293	1.000	0.788	0.023	0.024	0.341	1.000	0.591
29	rs2033529	0.055	0.083	0.507	0.034	0.058	0.560	-0.110	0.050	0.028	-0.005	0.056	0.923	-0.024	0.029	0.416	1.000	0.175	-0.035	0.031	0.262	1.000	0.140
30	rs2033732	0.022	0.056	0.691	-0.019	0.044	0.662	0.113	0.040	0.005	-0.050	0.043	0.243	0.020	0.022	0.364	1.000	**0.030**	0.020	0.024	0.414	1.000	**0.011**
31	rs205262	-0.002	0.076	0.978	-0.032	0.060	0.591	0.086	0.058	0.139	-0.068	0.062	0.273	-0.002	0.031	0.959	1.000	0.299	-0.002	0.035	0.965	1.000	0.159
32	rs2075650	-0.169	0.105	0.107	-0.165	0.077	0.032	0.056	0.069	0.419	0.038	0.076	0.617	-0.039	0.039	0.325	1.000	**0.068**	-0.017	0.043	0.684	1.000	**0.069**
33	rs2080454	0.061	0.059	0.306	0.037	0.042	0.387	-0.077	0.039	0.046	-0.032	0.043	0.456	-0.015	0.022	0.489	1.000	0.117	-0.027	0.024	0.248	1.000	0.137
34	rs2112347	0.036	0.056	0.523	0.015	0.042	0.725	-0.025	0.039	0.526	0.029	0.043	0.493	0.009	0.022	0.668	1.000	0.748	0.005	0.024	0.846	1.000	0.619
35	rs2176040	0.086	0.109	0.427	0.101	0.082	0.222	0.148	0.076	0.052	0.020	0.081	0.804	0.091	0.042	0.032	1.000	0.720	0.092	0.046	0.046	1.000	0.513
36	rs2207139	0.039	0.077	0.611	0.020	0.061	0.741	0.022	0.061	0.721	-0.045	0.062	0.469	0.007	0.032	0.840	1.000	0.806	-3.65E-04	0.035	0.992	1.000	0.683
37	rs2287019	-0.006	0.071	0.931	0.033	0.053	0.533	0.037	0.049	0.449	0.010	0.057	0.857	0.023	0.028	0.415	1.000	0.953	0.028	0.030	0.355	1.000	0.932
38	rs2365389	0.127	0.080	0.114	-0.047	0.060	0.434	-0.036	0.062	0.563	-0.030	0.063	0.638	-0.011	0.033	0.743	1.000	0.313	-0.038	0.036	0.289	1.000	0.978
39	rs2820292	-4.85E-04	0.068	0.994	-0.071	0.055	0.194	-0.003	0.049	0.946	-0.056	0.053	0.284	-0.034	0.028	0.211	1.000	0.735	-0.041	0.030	0.172	1.000	0.614
40	rs2836754	0.004	0.059	0.945	-0.064	0.043	0.136	0.033	0.040	0.404	0.031	0.045	0.484	0.002	0.023	0.943	1.000	0.331	0.001	0.024	0.961	1.000	0.181
41	rs29941	0.050	0.072	0.484	-0.025	0.050	0.618	0.006	0.049	0.902	0.038	0.053	0.474	0.012	0.027	0.667	1.000	0.782	0.005	0.029	0.857	1.000	0.689
42	rs3101336	-0.087	0.108	0.418	-0.057	0.077	0.459	-0.045	0.069	0.515	-0.031	0.081	0.705	-0.051	0.040	0.208	1.000	0.979	-0.045	0.044	0.303	1.000	0.972
43	rs3817334	-0.050	0.062	0.422	-0.008	0.046	0.861	0.004	0.044	0.925	-0.017	0.048	0.722	-0.013	0.024	0.590	1.000	0.914	-0.006	0.026	0.809	1.000	0.947
44	rs3849570	0.037	0.056	0.508	0.038	0.042	0.376	-0.031	0.039	0.415	-0.052	0.043	0.225	-0.008	0.022	0.716	1.000	0.358	-0.016	0.024	0.500	1.000	0.291
45	rs3888190	-0.102	0.099	0.301	-0.024	0.075	0.754	-0.029	0.069	0.671	0.032	0.076	0.674	-0.023	0.039	0.552	1.000	0.760	-0.009	0.042	0.838	1.000	0.813
46	rs4256980	0.073	0.060	0.222	0.018	0.042	0.664	-0.023	0.040	0.557	-0.041	0.043	0.347	-0.003	0.022	0.895	1.000	0.408	-0.015	0.024	0.525	1.000	0.602

Table 45 (continued): Association between 64 SNPs and %MFA intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	-0.116	0.064	0.071	-0.053	0.049	0.280	0.036	0.044	0.414	0.012	0.051	0.820	-0.018	0.025	0.488	1.000	0.197	0.001	0.028	0.977	1.000	0.390
48	rs4787491	0.056	0.058	0.329	0.009	0.041	0.827	0.018	0.040	0.649	-0.014	0.043	0.744	0.013	0.022	0.566	1.000	0.805	0.005	0.024	0.827	1.000	0.855
49	rs492400	-0.003	0.072	0.962	-0.053	0.051	0.296	-0.019	0.047	0.689	-0.021	0.051	0.681	-0.027	0.026	0.315	1.000	0.937	-0.030	0.028	0.288	1.000	0.862
50	rs6567160	0.049	0.078	0.528	0.036	0.055	0.517	0.141	0.053	0.008	0.031	0.059	0.594	0.069	0.029	0.019	1.000	0.438	0.073	0.032	0.022	1.000	0.268
51	rs6804842	0.028	0.060	0.643	0.023	0.045	0.614	0.049	0.042	0.242	-0.067	0.044	0.128	0.007	0.023	0.779	1.000	0.252	0.003	0.025	0.914	1.000	0.140
52	rs7138803	-0.081	0.066	0.225	0.069	0.048	0.152	0.006	0.044	0.884	-0.012	0.050	0.805	0.006	0.025	0.802	1.000	0.315	0.021	0.027	0.442	1.000	0.463
53	rs7141420	-0.027	0.056	0.632	0.016	0.042	0.707	0.047	0.039	0.231	0.062	0.042	0.139	0.032	0.022	0.147	1.000	0.593	0.042	0.024	0.076	1.000	0.729
54	rs7164727	-0.096	0.066	0.147	-0.030	0.048	0.531	-0.004	0.045	0.925	0.064	0.048	0.184	-0.006	0.025	0.812	1.000	0.238	0.009	0.027	0.734	1.000	0.357
55	rs7239883	0.002	0.062	0.975	-0.007	0.045	0.883	0.021	0.042	0.618	-0.070	0.046	0.131	-0.013	0.024	0.578	1.000	0.522	-0.016	0.025	0.539	1.000	0.336
56	rs7243357	0.108	0.069	0.115	-0.020	0.051	0.697	4.42E-05	0.052	0.999	-0.020	0.052	0.697	0.006	0.027	0.831	1.000	0.433	-0.013	0.030	0.652	1.000	0.951
57	rs7599312	0.135	0.216	0.533	-0.017	0.156	0.911	-0.071	0.120	0.555	-0.106	0.151	0.485	-0.042	0.075	0.578	1.000	0.818	-0.066	0.080	0.409	1.000	0.919
58	rs7715256	-0.237	0.149	0.111	-0.036	0.113	0.750	0.026	0.111	0.818	0.045	0.109	0.680	-0.027	0.059	0.649	1.000	0.446	0.012	0.064	0.846	1.000	0.866
59	rs7903146	0.142	0.195	0.468	-0.246	0.132	0.062	-0.105	0.140	0.452	-0.042	0.144	0.773	-0.098	0.074	0.187	1.000	0.402	-0.138	0.080	0.085	1.000	0.556
60	rs9374842	-0.198	0.105	0.060	0.078	0.072	0.276	-0.028	0.069	0.682	-9.24E-05	0.075	0.999	-0.013	0.039	0.739	1.000	0.186	0.016	0.041	0.699	1.000	0.547
61	rs9400239	0.099	0.063	0.114	-0.009	0.046	0.849	-0.048	0.043	0.259	0.037	0.048	0.449	0.006	0.024	0.801	1.000	0.228	-0.010	0.026	0.695	1.000	0.420
62	rs9641123	0.039	0.062	0.526	0.037	0.045	0.413	0.051	0.042	0.221	-0.044	0.046	0.340	0.020	0.023	0.386	1.000	0.435	0.017	0.025	0.499	1.000	0.269
63	rs977747	-0.123	0.156	0.429	-0.098	0.108	0.366	-0.065	0.104	0.532	-0.030	0.097	0.758	-0.070	0.055	0.210	1.000	0.949	-0.062	0.059	0.298	1.000	0.896
64	rs9914578	0.059	0.070	0.399	-0.007	0.051	0.896	0.035	0.050	0.486	-0.004	0.055	0.949	0.017	0.027	0.538	1.000	0.840	0.009	0.030	0.758	1.000	0.814

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

6.3.6.9 %PFA

After meta-analysis, nominal significance were found between rs11030104 on *BDNF* (β=-0.049, SE=0.022, P=0.026), rs11126666 on *KCNK3* (β=-0.063, SE=0.024, P=0.010), rs17203016 on *CREB1* (β=-0.108, SE=0.032, P=0.001), rs2080454 on *CBLN1* (β=0.052, SE=0.023, P=0.022) and rs9374842 on *LOC285762* (β=-0.089, SE=0.040, P=0.024) and intake of %PFA (Table 46). BMI risk allele A of rs11030104, A of rs11126666, G of rs17203016 and T of rs9374842 would decrease while C of rs2080454 would increase intake of %PFA.

6.3.6.10 %Carbohydrate

After meta-analysis, nominal significance were found between rs11126666 on *KCNK3* (β=0.070, SE=0.024, P=0.003) and rs3101336 on *NEGR1* (β=0.089, SE=0.040, P=0.026) and intake of %carbohydrate (Table 47). BMI risk allele A of rs11126666 and C of rs3101336 were all positively associated with %carbohydrate intake.

6.3.7 Interaction between 64 SNPs and dietary intake for BMI

We tested each of the 64 BMI risk loci for interaction with various dietary components intake in each cohort individually and subsequently meta-analyzed.

Table 46: Association between 64 SNPs and %PFA intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	0.008	0.059	0.897	0.023	0.044	0.600	-0.045	0.041	0.271	-0.073	0.046	0.113	-0.025	0.023	0.271	1.000	0.421	-0.031	0.025	0.211	1.000	0.294
2	rs1016287	-0.030	0.063	0.638	0.055	0.048	0.247	-0.048	0.048	0.318	0.012	0.049	0.803	0.001	0.026	0.978	1.000	0.454	0.007	0.028	0.812	1.000	0.310
3	rs10182181	0.089	0.058	0.124	0.036	0.043	0.410	0.029	0.041	0.487	-0.003	0.044	0.940	0.031	0.023	0.167	1.000	0.651	0.021	0.025	0.399	1.000	0.796
4	rs10733682	0.040	0.065	0.537	-0.017	0.051	0.733	-0.040	0.046	0.391	-0.018	0.054	0.737	-0.015	0.026	0.561	1.000	0.799	-0.026	0.029	0.362	1.000	0.934
5	rs10938397	0.067	0.064	0.298	-0.015	0.048	0.760	-0.011	0.046	0.805	-0.170	0.050	0.001	-0.040	0.025	0.113	1.000	**0.018**	-0.060	0.028	0.030	1.000	**0.034**
6	rs10968576	-0.006	0.077	0.940	0.004	0.057	0.947	0.002	0.053	0.967	0.027	0.059	0.648	0.008	0.030	0.795	1.000	0.985	0.010	0.032	0.753	1.000	0.943
7	rs11030104	-0.058	0.056	0.298	-0.102	0.041	0.014	-0.053	0.040	0.188	0.020	0.043	0.650	-0.049	0.022	0.026	1.000	0.241	-0.047	0.024	0.049	1.000	0.125
8	rs11126666	-0.112	0.061	0.068	-0.100	0.046	0.028	-0.030	0.045	0.498	-0.027	0.048	0.569	-0.063	0.024	0.010	0.640	0.498	-0.053	0.027	0.045	1.000	0.448
9	rs11191560	0.047	0.066	0.477	-0.004	0.048	0.939	-0.028	0.045	0.528	0.020	0.051	0.700	0.002	0.026	0.947	1.000	0.788	-0.006	0.028	0.821	1.000	0.778
10	rs11583200	0.141	0.094	0.133	-0.049	0.078	0.526	-0.052	0.076	0.494	-0.121	0.086	0.159	-0.030	0.041	0.469	1.000	0.204	-0.071	0.046	0.123	1.000	0.785
11	rs11688816	0.109	0.062	0.081	0.061	0.047	0.199	-0.014	0.044	0.751	-0.030	0.049	0.535	0.021	0.025	0.386	1.000	0.218	0.005	0.027	0.848	1.000	0.350
12	rs12286929	-0.073	0.068	0.284	-0.002	0.047	0.961	-0.026	0.046	0.569	0.024	0.049	0.629	-0.012	0.025	0.624	1.000	0.689	-0.003	0.027	0.924	1.000	0.759
13	rs12429545	-0.003	0.068	0.962	0.035	0.047	0.461	-0.009	0.047	0.845	0.045	0.053	0.398	0.018	0.026	0.487	1.000	0.846	0.022	0.028	0.439	1.000	0.706
14	rs12566985	-0.176	0.073	0.016	0.105	0.055	0.058	0.024	0.053	0.652	0.005	0.059	0.937	0.010	0.029	0.741	1.000	**0.024**	0.045	0.032	0.157	1.000	0.406
15	rs12940622	-0.056	0.062	0.362	0.082	0.047	0.078	0.038	0.044	0.386	-0.017	0.047	0.720	0.021	0.024	0.389	1.000	0.252	0.035	0.026	0.184	1.000	0.326
16	rs13021737	0.032	0.113	0.780	0.064	0.081	0.426	-0.085	0.075	0.259	0.119	0.088	0.177	0.024	0.043	0.584	1.000	0.320	0.022	0.047	0.633	1.000	0.173
17	rs13201877	-0.244	0.181	0.178	-0.141	0.106	0.183	-0.002	0.104	0.988	-0.098	0.115	0.391	-0.096	0.059	0.103	1.000	0.644	-0.079	0.062	0.208	1.000	0.630
18	rs1441264	0.005	0.060	0.938	-0.100	0.043	0.022	0.026	0.041	0.518	-0.027	0.045	0.554	-0.026	0.023	0.264	1.000	0.185	-0.031	0.025	0.214	1.000	0.104
19	rs1460676	-0.011	0.059	0.848	0.038	0.045	0.401	-0.008	0.041	0.854	0.051	0.045	0.257	0.019	0.023	0.405	1.000	0.713	0.025	0.025	0.323	1.000	0.591
20	rs1516725	-0.030	0.105	0.773	-0.013	0.084	0.879	0.037	0.072	0.610	-0.071	0.083	0.391	-0.014	0.042	0.743	1.000	0.802	-0.011	0.046	0.817	1.000	0.617
21	rs1528435	0.002	0.062	0.976	-0.014	0.045	0.759	-0.040	0.043	0.357	0.014	0.047	0.769	-0.012	0.024	0.611	1.000	0.856	-0.015	0.026	0.572	1.000	0.701
22	rs1558902	0.011	0.082	0.894	-0.014	0.063	0.821	-0.042	0.063	0.507	-0.025	0.071	0.726	-0.021	0.034	0.551	1.000	0.964	-0.027	0.038	0.472	1.000	0.952
23	rs16851483	-0.009	0.064	0.889	0.058	0.049	0.241	0.045	0.046	0.333	0.042	0.052	0.414	0.039	0.026	0.131	1.000	0.868	0.048	0.028	0.087	1.000	0.971

Table 46 (continued): Association between 64 SNPs and %PFA intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	-3.04E-04	0.060	0.996	-0.018	0.042	0.664	0.019	0.041	0.641	0.027	0.045	0.549	0.007	0.023	0.748	1.000	0.882	0.009	0.024	0.728	1.000	0.725
25	rs17203016	-0.183	0.086	0.033	0.060	0.062	0.332	-0.119	0.057	0.035	-0.226	0.063	3.30E-04	-0.108	0.032	0.001	0.064	**0.008**	-0.095	0.035	0.006	0.384	**0.004**
26	rs17405819	-0.015	0.059	0.806	0.006	0.043	0.898	-0.001	0.041	0.989	0.023	0.044	0.609	0.005	0.023	0.821	1.000	0.962	0.009	0.025	0.728	1.000	0.925
27	rs17724992	-0.027	0.056	0.634	0.059	0.043	0.173	0.017	0.040	0.671	-0.027	0.044	0.546	0.010	0.022	0.650	1.000	0.488	0.017	0.024	0.483	1.000	0.384
28	rs1928295	-0.033	0.058	0.573	-0.114	0.044	0.009	-0.035	0.040	0.377	0.077	0.045	0.089	-0.028	0.023	0.219	1.000	**0.025**	-0.027	0.025	0.273	1.000	**0.009**
29	rs2033529	0.009	0.084	0.916	0.080	0.059	0.176	-0.091	0.052	0.077	0.024	0.059	0.680	-0.003	0.030	0.929	1.000	0.162	-0.004	0.032	0.891	1.000	**0.078**
30	rs2033732	0.042	0.057	0.460	-0.027	0.044	0.543	-0.063	0.041	0.126	0.029	0.044	0.517	-0.012	0.023	0.595	1.000	0.334	-0.023	0.025	0.366	1.000	0.314
31	rs205262	-0.035	0.077	0.649	-0.027	0.061	0.658	-0.039	0.060	0.512	-0.122	0.064	0.057	-0.056	0.032	0.083	1.000	0.696	-0.060	0.036	0.089	1.000	0.510
32	rs2075650	-0.195	0.106	0.066	0.062	0.078	0.429	-0.035	0.071	0.622	-0.010	0.079	0.897	-0.026	0.040	0.522	1.000	0.278	0.003	0.044	0.947	1.000	0.644
33	rs2080454	0.057	0.060	0.340	0.062	0.043	0.148	0.039	0.040	0.332	0.053	0.044	0.232	0.052	0.023	0.022	1.000	0.983	0.051	0.024	0.038	1.000	0.924
34	rs2112347	-0.089	0.056	0.116	0.008	0.043	0.852	-0.007	0.040	0.856	-0.057	0.044	0.200	-0.029	0.023	0.200	1.000	0.468	-0.018	0.025	0.475	1.000	0.548
35	rs2176040	0.092	0.110	0.400	-0.012	0.084	0.888	0.062	0.079	0.427	-0.111	0.084	0.186	0.001	0.043	0.989	1.000	0.374	-0.016	0.047	0.728	1.000	0.319
36	rs2207139	0.108	0.078	0.165	0.094	0.062	0.129	0.078	0.063	0.214	-0.056	0.065	0.393	0.054	0.033	0.105	1.000	0.273	0.041	0.036	0.256	1.000	0.193
37	rs2287019	-0.008	0.072	0.908	0.024	0.054	0.660	0.044	0.051	0.382	0.117	0.059	0.047	0.047	0.029	0.099	1.000	0.531	0.058	0.031	0.064	1.000	0.475
38	rs2365389	0.132	0.081	0.102	-0.078	0.062	0.204	-0.054	0.064	0.397	0.016	0.065	0.812	-0.011	0.033	0.741	1.000	0.175	-0.041	0.037	0.268	1.000	0.560
39	rs2820292	0.043	0.069	0.532	-0.150	0.056	0.008	0.015	0.051	0.773	-0.044	0.055	0.424	-0.038	0.028	0.178	1.000	**0.092**	-0.055	0.031	0.079	1.000	**0.091**
40	rs2836754	-0.031	0.059	0.601	-0.035	0.044	0.422	0.008	0.041	0.846	0.042	0.046	0.369	-0.002	0.023	0.945	1.000	0.623	0.004	0.025	0.883	1.000	0.479
41	rs29941	0.076	0.073	0.297	-0.017	0.051	0.747	-0.063	0.050	0.211	0.024	0.055	0.660	-0.007	0.028	0.810	1.000	0.408	-0.021	0.030	0.488	1.000	0.501
42	rs3101336	-0.117	0.108	0.281	-0.181	0.079	0.021	0.077	0.072	0.283	-0.064	0.084	0.447	-0.057	0.041	0.167	1.000	**0.097**	-0.047	0.045	0.294	1.000	**0.051**
43	rs3817334	0.010	0.062	0.878	0.026	0.047	0.576	0.023	0.045	0.614	0.007	0.049	0.880	0.018	0.025	0.476	1.000	0.991	0.019	0.027	0.477	1.000	0.958
44	rs3849570	-0.029	0.057	0.610	0.048	0.043	0.266	0.014	0.040	0.719	-0.029	0.045	0.510	0.006	0.022	0.803	1.000	0.573	0.012	0.024	0.623	1.000	0.459
45	rs3888190	-0.042	0.100	0.674	0.003	0.076	0.966	-0.029	0.071	0.681	0.057	0.079	0.470	-0.001	0.040	0.990	1.000	0.833	0.007	0.043	0.865	1.000	0.717
46	rs4256980	-0.049	0.060	0.418	0.017	0.043	0.701	0.014	0.041	0.740	0.061	0.045	0.176	0.018	0.023	0.439	1.000	0.541	0.029	0.025	0.242	1.000	0.696

Table 46 (continued): Association between 64 SNPs and %PFA intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	-0.098	0.064	0.130	-0.003	0.050	0.945	-0.017	0.046	0.709	0.012	0.053	0.827	-0.020	0.026	0.451	1.000	0.590	-0.004	0.029	0.877	1.000	0.920
48	rs4787491	0.045	0.058	0.435	0.016	0.041	0.696	0.040	0.041	0.329	0.002	0.044	0.969	0.024	0.022	0.284	1.000	0.903	0.020	0.024	0.405	1.000	0.813
49	rs492400	-0.126	0.072	0.081	-0.024	0.052	0.635	-0.006	0.048	0.902	-0.052	0.053	0.328	-0.040	0.027	0.138	1.000	0.561	-0.026	0.029	0.374	1.000	0.816
50	rs6567160	0.146	0.078	0.063	0.003	0.056	0.951	0.022	0.055	0.682	0.031	0.061	0.607	0.037	0.030	0.216	1.000	0.499	0.018	0.033	0.575	1.000	0.941
51	rs6804842	0.035	0.060	0.560	0.008	0.046	0.857	0.093	0.044	0.032	-0.081	0.046	0.077	0.014	0.024	0.570	1.000	**0.051**	0.010	0.026	0.713	1.000	**0.022**
52	rs7138803	-0.180	0.067	0.007	0.066	0.049	0.174	-0.021	0.046	0.647	0.016	0.052	0.751	-0.011	0.026	0.672	1.000	**0.026**	0.019	0.028	0.500	1.000	0.427
53	rs7141420	-0.017	0.057	0.761	-0.034	0.043	0.429	-0.021	0.041	0.598	0.027	0.043	0.531	-0.011	0.022	0.616	1.000	0.768	-0.010	0.024	0.677	1.000	0.570
54	rs7164727	-0.116	0.067	0.082	0.116	0.048	0.016	0.070	0.047	0.132	0.014	0.050	0.782	0.041	0.026	0.115	1.000	**0.034**	0.068	0.028	0.015	0.960	0.335
55	rs7239883	-0.090	0.062	0.150	0.014	0.046	0.752	0.043	0.043	0.315	0.013	0.048	0.784	0.007	0.024	0.756	1.000	0.366	0.025	0.026	0.345	1.000	0.863
56	rs7243357	-0.047	0.069	0.494	-0.016	0.051	0.757	0.020	0.054	0.714	-0.016	0.054	0.774	-0.011	0.028	0.687	1.000	0.892	-0.004	0.031	0.890	1.000	0.863
57	rs7599312	0.283	0.218	0.195	0.163	0.158	0.302	0.101	0.124	0.415	-0.146	0.157	0.353	0.079	0.077	0.309	1.000	0.356	0.049	0.083	0.551	1.000	0.326
58	rs7715256	-0.164	0.150	0.275	-0.068	0.115	0.555	-0.100	0.114	0.381	-0.011	0.114	0.922	-0.077	0.060	0.205	1.000	0.869	-0.060	0.066	0.367	1.000	0.856
59	rs7903146	-0.066	0.197	0.737	-0.139	0.134	0.299	-0.225	0.144	0.119	-0.002	0.151	0.989	-0.117	0.076	0.122	1.000	0.746	-0.126	0.082	0.125	1.000	0.563
60	rs9374842	-0.319	0.106	0.003	-0.089	0.073	0.223	-0.059	0.071	0.406	-0.002	0.078	0.984	-0.089	0.040	0.024	1.000	0.104	-0.052	0.043	0.222	1.000	0.710
61	rs9400239	0.043	0.064	0.500	-0.025	0.047	0.593	-0.017	0.044	0.699	-0.003	0.050	0.952	-0.007	0.025	0.788	1.000	0.844	-0.016	0.027	0.563	1.000	0.949
62	rs9641123	0.067	0.062	0.282	-0.010	0.046	0.835	0.028	0.043	0.521	-0.044	0.047	0.356	0.005	0.024	0.843	1.000	0.489	-0.006	0.026	0.812	1.000	0.535
63	rs977747	-0.062	0.157	0.695	-0.087	0.110	0.424	-0.016	0.107	0.881	0.073	0.101	0.469	-0.013	0.057	0.820	1.000	0.732	-0.006	0.061	0.927	1.000	0.555
64	rs9914578	0.103	0.070	0.141	0.052	0.052	0.314	-0.003	0.051	0.957	0.004	0.057	0.951	0.032	0.028	0.254	1.000	0.594	0.018	0.031	0.551	1.000	0.717

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

Table 47: Association between 64 SNPs and %Carbohydrate intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	-0.035	0.059	0.552	-0.049	0.043	0.262	-0.028	0.039	0.468	0.027	0.044	0.537	-0.020	0.022	0.365	1.000	0.637	-0.018	0.024	0.462	1.000	0.443
2	rs1016287	-0.015	0.062	0.815	-0.025	0.047	0.589	0.037	0.046	0.417	-0.008	0.047	0.856	-0.001	0.025	0.974	1.000	0.792	0.002	0.027	0.948	1.000	0.612
3	rs10182181	-0.081	0.057	0.154	0.031	0.043	0.470	-0.013	0.039	0.742	0.028	0.042	0.506	-3.74E-04	0.022	0.986	1.000	0.375	0.014	0.024	0.561	1.000	0.692
4	rs10733682	-0.050	0.064	0.434	-0.028	0.050	0.580	0.063	0.044	0.153	0.001	0.052	0.992	0.006	0.026	0.806	1.000	0.406	0.017	0.028	0.544	1.000	0.371
5	rs10938397	-0.056	0.063	0.374	0.044	0.047	0.348	0.048	0.044	0.273	0.087	0.048	0.070	0.041	0.024	0.091	1.000	0.347	0.059	0.027	0.027	1.000	0.777
6	rs10968576	0.014	0.075	0.854	-0.035	0.056	0.529	-0.042	0.050	0.399	0.023	0.056	0.679	-0.015	0.029	0.598	1.000	0.792	-0.020	0.031	0.518	1.000	0.650
7	rs11030104	0.008	0.055	0.889	0.064	0.041	0.117	-0.024	0.038	0.533	-0.027	0.041	0.514	0.004	0.021	0.851	1.000	0.354	0.003	0.023	0.885	1.000	0.197
8	rs11126666	0.140	0.060	0.020	0.055	0.045	0.223	0.058	0.043	0.178	0.059	0.046	0.197	0.070	0.024	0.003	0.192	0.658	0.057	0.026	0.026	1.000	0.998
9	rs11191560	-0.068	0.065	0.290	0.015	0.048	0.745	0.023	0.042	0.587	0.036	0.049	0.461	0.011	0.025	0.652	1.000	0.602	0.025	0.027	0.356	1.000	0.955
10	rs11583200	-0.083	0.092	0.370	0.131	0.077	0.089	0.037	0.072	0.610	0.089	0.082	0.277	0.052	0.040	0.190	1.000	0.329	0.083	0.044	0.060	1.000	0.666
11	rs11688816	-0.027	0.062	0.667	-0.008	0.047	0.855	0.038	0.042	0.367	0.021	0.046	0.653	0.012	0.024	0.627	1.000	0.802	0.018	0.026	0.479	1.000	0.760
12	rs12286929	0.052	0.067	0.434	-0.037	0.047	0.425	-0.004	0.044	0.924	-0.044	0.047	0.345	-0.017	0.025	0.494	1.000	0.641	-0.028	0.026	0.297	1.000	0.798
13	rs12429545	-0.029	0.067	0.670	0.013	0.046	0.784	-0.023	0.045	0.612	0.041	0.051	0.417	0.003	0.025	0.915	1.000	0.762	0.008	0.027	0.772	1.000	0.635
14	rs12566985	5.90E-05	0.072	0.999	-0.112	0.054	0.039	-0.057	0.050	0.254	0.067	0.056	0.231	-0.031	0.028	0.267	1.000	0.124	-0.037	0.031	0.228	1.000	**0.063**
15	rs12940622	0.058	0.061	0.339	-0.034	0.046	0.453	-0.059	0.041	0.154	-0.014	0.045	0.755	-0.023	0.023	0.325	1.000	0.449	-0.037	0.025	0.142	1.000	0.761
16	rs13021737	-0.025	0.111	0.818	-0.130	0.079	0.100	-0.042	0.072	0.560	-0.096	0.084	0.252	-0.078	0.042	0.062	1.000	0.812	-0.086	0.045	0.055	1.000	0.707
17	rs13201877	0.245	0.178	0.170	-0.069	0.104	0.510	-0.015	0.100	0.883	0.122	0.109	0.265	0.033	0.057	0.564	1.000	0.354	0.009	0.060	0.884	1.000	0.431
18	rs1441264	0.010	0.059	0.866	0.038	0.043	0.377	-0.039	0.038	0.317	0.039	0.043	0.360	0.009	0.022	0.676	1.000	0.480	0.009	0.024	0.702	1.000	0.290
19	rs1460676	-0.019	0.058	0.748	-0.043	0.044	0.323	0.010	0.039	0.807	-0.030	0.043	0.494	-0.019	0.022	0.402	1.000	0.824	-0.019	0.024	0.439	1.000	0.636
20	rs1516725	0.121	0.103	0.239	-0.044	0.083	0.598	-0.070	0.068	0.303	0.049	0.079	0.533	-0.003	0.040	0.932	1.000	0.375	-0.026	0.044	0.552	1.000	0.503
21	rs1528435	-0.061	0.061	0.322	-0.060	0.044	0.172	0.011	0.041	0.794	-0.037	0.044	0.408	-0.032	0.023	0.170	1.000	0.631	-0.027	0.025	0.281	1.000	0.482
22	rs1558902	-0.007	0.080	0.927	-0.055	0.062	0.377	0.026	0.060	0.660	-0.010	0.068	0.883	-0.011	0.033	0.735	1.000	0.828	-0.012	0.036	0.742	1.000	0.641
23	rs16851483	0.054	0.063	0.391	-0.065	0.048	0.177	-0.003	0.044	0.953	-0.020	0.049	0.679	-0.015	0.025	0.550	1.000	0.498	-0.028	0.027	0.308	1.000	0.619

Table 47 (continued): Association between 64 SNPs and %Carbohydrate intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	0.038	0.059	0.514	0.016	0.041	0.696	-0.011	0.039	0.780	-0.014	0.043	0.735	0.003	0.022	0.902	1.000	0.860	-0.003	0.024	0.897	1.000	0.848
25	rs17203016	0.081	0.085	0.338	0.035	0.061	0.569	-0.027	0.054	0.613	0.021	0.060	0.721	0.017	0.031	0.592	1.000	0.719	0.007	0.033	0.843	1.000	0.716
26	rs17405819	0.077	0.058	0.183	-0.025	0.043	0.549	-0.060	0.039	0.120	0.010	0.042	0.812	-0.012	0.022	0.571	1.000	0.231	-0.027	0.024	0.247	1.000	0.472
27	rs17724992	0.007	0.056	0.904	-0.031	0.043	0.463	-0.040	0.038	0.290	0.033	0.042	0.430	-0.011	0.022	0.596	1.000	0.569	-0.015	0.023	0.531	1.000	0.389
28	rs1928295	-0.004	0.057	0.949	0.022	0.043	0.606	-0.029	0.038	0.442	-0.051	0.043	0.235	-0.018	0.022	0.418	1.000	0.656	-0.020	0.024	0.395	1.000	0.462
29	rs2033529	-0.048	0.082	0.561	-0.055	0.058	0.344	0.122	0.049	0.013	-0.052	0.056	0.353	0.009	0.029	0.760	1.000	**0.042**	0.017	0.031	0.585	1.000	**0.022**
30	rs2033732	0.008	0.056	0.881	0.017	0.044	0.692	-0.033	0.039	0.402	0.077	0.042	0.066	0.017	0.022	0.450	1.000	0.296	0.018	0.024	0.449	1.000	0.159
31	rs205262	0.036	0.076	0.634	0.078	0.060	0.190	0.007	0.057	0.896	0.115	0.061	0.060	0.059	0.031	0.056	1.000	0.604	0.064	0.034	0.060	1.000	0.420
32	rs2075650	0.140	0.104	0.180	0.087	0.077	0.258	-0.012	0.067	0.858	-0.114	0.075	0.129	0.007	0.039	0.853	1.000	0.145	-0.014	0.042	0.732	1.000	0.173
33	rs2080454	-0.035	0.059	0.547	-0.034	0.042	0.415	0.031	0.038	0.420	-0.006	0.042	0.884	-0.006	0.022	0.795	1.000	0.652	-0.001	0.024	0.969	1.000	0.512
34	rs2112347	0.017	0.056	0.760	0.024	0.042	0.577	0.014	0.038	0.720	0.001	0.042	0.982	0.013	0.022	0.535	1.000	0.985	0.013	0.024	0.586	1.000	0.930
35	rs2176040	0.017	0.108	0.874	-0.082	0.082	0.317	-0.092	0.075	0.217	0.014	0.080	0.864	-0.044	0.042	0.293	1.000	0.687	-0.055	0.045	0.228	1.000	0.577
36	rs2207139	-0.052	0.076	0.493	-0.015	0.061	0.806	-0.008	0.060	0.887	0.021	0.062	0.731	-0.010	0.032	0.754	1.000	0.903	-0.001	0.035	0.976	1.000	0.906
37	rs2287019	0.048	0.070	0.492	-0.048	0.053	0.367	-0.057	0.048	0.238	-0.043	0.056	0.447	-0.035	0.028	0.209	1.000	0.641	-0.050	0.030	0.097	1.000	0.981
38	rs2365389	-0.079	0.079	0.323	0.094	0.061	0.123	-0.044	0.061	0.464	0.007	0.062	0.906	0.003	0.032	0.926	1.000	0.271	0.019	0.035	0.589	1.000	0.266
39	rs2820292	0.002	0.068	0.979	0.084	0.055	0.127	-0.012	0.048	0.795	0.023	0.052	0.654	0.023	0.027	0.393	1.000	0.601	0.027	0.030	0.357	1.000	0.418
40	rs2836754	0.023	0.058	0.692	0.049	0.043	0.260	0.007	0.039	0.850	-0.037	0.044	0.396	0.009	0.022	0.679	1.000	0.569	0.007	0.024	0.777	1.000	0.377
41	rs29941	-0.094	0.071	0.188	0.029	0.050	0.569	0.041	0.048	0.387	-0.031	0.052	0.548	-4.10E-04	0.027	0.988	1.000	0.366	0.015	0.029	0.606	1.000	0.557
42	rs3101336	0.157	0.107	0.143	0.169	0.077	0.028	0.020	0.068	0.771	0.059	0.080	0.465	0.089	0.040	0.026	1.000	0.445	0.078	0.043	0.072	1.000	0.334
43	rs3817334	0.070	0.061	0.256	-0.011	0.046	0.818	-0.048	0.043	0.266	-0.016	0.047	0.725	-0.011	0.024	0.633	1.000	0.480	-0.026	0.026	0.317	1.000	0.815
44	rs3849570	-0.030	0.056	0.597	-0.036	0.042	0.397	0.014	0.038	0.705	0.014	0.042	0.750	-0.006	0.022	0.795	1.000	0.759	-0.001	0.023	0.953	1.000	0.619
45	rs3888190	0.089	0.098	0.365	0.036	0.075	0.627	0.047	0.067	0.482	0.001	0.075	0.987	0.039	0.038	0.311	1.000	0.913	0.03	0.042	0.474	1.000	0.896
46	rs4256980	-0.043	0.059	0.468	0.026	0.042	0.544	0.022	0.039	0.566	-0.019	0.043	0.656	0.003	0.022	0.887	1.000	0.705	0.011	0.024	0.658	1.000	0.704

Table 47 (continued): Association between 64 SNPs and %Carbohydrate intake

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	0.167	0.063	0.008	0.048	0.049	0.333	-0.018	0.043	0.685	-0.048	0.051	0.340	0.021	0.025	0.405	1.000	**0.040**	-0.006	0.027	0.813	1.000	0.375
48	rs4787491	0.013	0.057	0.817	0.009	0.041	0.819	-0.012	0.039	0.757	0.059	0.042	0.162	0.016	0.022	0.451	1.000	0.660	0.017	0.023	0.472	1.000	0.451
49	rs492400	0.023	0.071	0.743	0.038	0.051	0.453	-0.009	0.046	0.852	-0.021	0.050	0.679	0.005	0.026	0.853	1.000	0.839	0.002	0.028	0.945	1.000	0.682
50	rs6567160	-0.090	0.077	0.243	-0.008	0.055	0.879	-0.066	0.052	0.204	-0.022	0.058	0.700	-0.042	0.029	0.152	1.000	0.778	-0.034	0.031	0.284	1.000	0.726
51	rs6804842	-0.090	0.059	0.131	-0.016	0.045	0.720	-0.067	0.041	0.104	0.088	0.043	0.042	-0.014	0.023	0.552	1.000	**0.031**	-2.31E-04	0.025	0.993	1.000	**0.031**
52	rs7138803	0.132	0.066	0.047	-0.039	0.048	0.411	-0.001	0.044	0.973	0.031	0.049	0.523	0.016	0.025	0.530	1.000	0.199	-0.004	0.027	0.895	1.000	0.586
53	rs7141420	0.016	0.056	0.769	-0.035	0.042	0.409	-0.007	0.038	0.849	-0.031	0.041	0.449	-0.018	0.022	0.415	1.000	0.870	-0.023	0.023	0.315	1.000	0.868
54	rs7164727	0.126	0.065	0.054	-0.001	0.047	0.986	0.020	0.045	0.652	-0.064	0.047	0.177	0.007	0.025	0.791	1.000	0.128	-0.013	0.027	0.615	1.000	0.412
55	rs7239883	0.005	0.061	0.940	-0.006	0.045	0.887	-0.040	0.041	0.321	0.035	0.045	0.441	-0.005	0.023	0.827	1.000	0.669	-0.007	0.025	0.790	1.000	0.465
56	rs7243357	-0.060	0.068	0.378	-0.017	0.050	0.732	-0.056	0.051	0.273	-0.024	0.051	0.643	-0.037	0.027	0.174	1.000	0.925	-0.032	0.029	0.272	1.000	0.848
57	rs7599312	-0.006	0.215	0.977	0.009	0.155	0.952	-0.024	0.117	0.836	0.171	0.149	0.252	0.034	0.074	0.646	1.000	0.765	0.040	0.079	0.617	1.000	0.574
58	rs7715256	0.290	0.149	0.052	0.001	0.113	0.990	0.117	0.108	0.280	-0.020	0.108	0.856	0.073	0.058	0.209	1.000	0.330	0.034	0.063	0.593	1.000	0.632
59	rs7903146	-0.188	0.194	0.331	0.176	0.132	0.180	0.200	0.137	0.143	0.109	0.142	0.446	0.113	0.073	0.121	1.000	0.382	0.164	0.079	0.038	1.000	0.891
60	rs9374842	0.248	0.104	0.018	-0.060	0.071	0.399	0.040	0.067	0.552	-0.012	0.074	0.876	0.026	0.038	0.499	1.000	**0.098**	-0.009	0.041	0.835	1.000	0.592
61	rs9400239	-0.112	0.062	0.072	0.026	0.046	0.573	0.047	0.042	0.263	0.014	0.048	0.770	0.009	0.024	0.701	1.000	0.190	0.031	0.026	0.241	1.000	0.868
62	rs9641123	-0.075	0.061	0.219	-0.018	0.045	0.694	-0.020	0.041	0.622	0.013	0.045	0.772	-0.019	0.023	0.422	1.000	0.717	-0.009	0.025	0.717	1.000	0.839
63	rs977747	0.119	0.154	0.443	0.205	0.107	0.057	0.075	0.102	0.464	0.004	0.096	0.965	0.091	0.055	0.096	1.000	0.572	0.087	0.059	0.137	1.000	0.374
64	rs9914578	-0.040	0.069	0.566	0.007	0.051	0.898	-0.006	0.049	0.903	-0.005	0.054	0.932	-0.007	0.027	0.788	1.000	0.961	-0.001	0.030	0.963	1.000	0.982

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant associations ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

Results are summarized and displayed in Table 48 to Table 58. The interaction between %fat and rs205262 (*C6orf106*) (β=0.122, SE=0.033, adjusted $P_{interaction}$=0.015), %SFA and rs11126666 (*KCNK3*) (β=-0.086, SE=0.025, adjusted $P_{interaction}$=0.044) and cholesterol and rs4740619 (*CCDC171*) (β=0.094, SE=0.027, adjusted $P_{interaction}$ =0.047) on BMI remained significant after correction for multiple testing (P<0.0007=0.05/74 tests).

6.3.7.1 Total calories

Table 48 shows the interaction results between 64 SNPs and total calories intake on Z-BMI. None of the interaction remained statistically significant after adjusting for multiple testing. Nominal significant negative SNP × calories interaction on BMI was observed for *GNPDA2* rs10938397 (β=-0.056, SE=0.026, $P_{interaction}$=0.033) and *NRXN3* rs7141420 (β=-0.057, SE=0.023, $P_{interaction}$= 0.014). The BMI level decreased as the number of reported BMI risk alleles and calories intake increased.

6.3.7.2 Cholesterol

Table 49 shows the interaction results between 64 SNPs and cholesterol intake on Z-BMI. Nominal significant SNP × cholesterol interaction on BMI was observed for *RABEP1* rs1000940 (β=-0.056, SE=0.024, $P_{interaction}$=0.020), *TDRG1* rs2033529 (β=-0.092, SE=0.032, $P_{interaction}$=0.004), *C6orf106* rs205262 (β=0.080, SE=0.033, $P_{interaction}$=0.017), *ETS2* rs2836754 (β=-0.052, SE=0.024, $P_{interaction}$=0.030) and *NEGR1* rs3101336 (β=-0.092, SE=0.042, $P_{interaction}$=0.029). In the case of rs205262, the

interaction term was found to be positively associated with Z-BMI. Thus BMI level increased as the number of G allele and the intake of total calories increased. For the rest SNPs, the interaction terms were negatively associated with Z-BMI so that the BMI level decreased as the number of reported BMI risk alleles and the intake of cholesterol increased.

The interaction effect of *CCDC171* rs4740619 with cholesterol was found to be significant on Z-BMI even after adjusting for multiple comparisons (β=0.094, SE=0.027, $P_{interaction}=6.40\times10^{-4}$, adjusted $P_{interaction}$ =0.047). The positive association between cholesterol intake and BMI tended to be stronger among individuals who are homozygous for the reported BMI risk allele T of *CCDC171* rs4740619 as compared to individuals who have less copies of the T allele. Figure 13 showed the association between rs4740619 and BMI depending on cholesterol intake using population mean as the cut-off (Mean ± SD: 216.33 ± 135.96 mg/day).

Figure 13: Association of *CCDC171* rs4740619 on BMI stratified by cholesterol intake

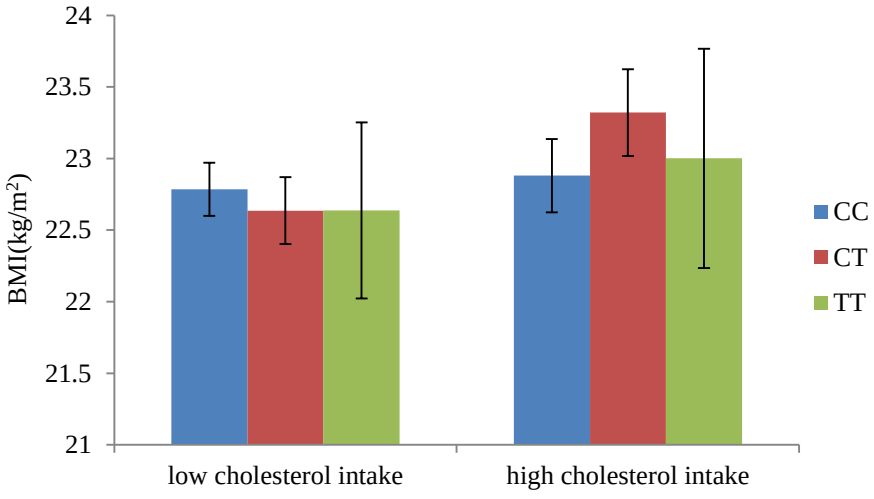


Table 48: Interaction between 64 SNPs and calories intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	0.091	0.064	0.153	0.044	0.045	0.329	0.040	0.042	0.342	-0.013	0.049	0.786	0.036	0.024	0.139	1.000	0.617	0.026	0.026	0.310	1.000	0.637
2	rs1016287	0.131	0.061	0.033	-0.050	0.049	0.303	-0.027	0.052	0.604	0.030	0.052	0.570	0.010	0.027	0.693	1.000	0.108	-0.018	0.030	0.553	1.000	0.521
3	rs10182181	4.03E-04	0.056	0.994	0.006	0.045	0.885	0.005	0.044	0.902	-0.045	0.045	0.323	-0.009	0.023	0.714	1.000	0.830	-0.010	0.026	0.684	1.000	0.654
4	rs10733682	0.085	0.068	0.213	-0.081	0.053	0.125	0.003	0.047	0.942	-0.039	0.056	0.484	-0.016	0.027	0.553	1.000	0.255	-0.035	0.030	0.235	1.000	0.485
5	rs10938397	0.004	0.066	0.957	-0.109	0.048	0.022	-0.037	0.049	0.451	-0.053	0.054	0.323	-0.056	0.026	0.033	1.000	0.529	-0.068	0.029	0.019	1.000	0.540
6	rs10968576	0.011	0.075	0.882	-0.068	0.055	0.216	0.053	0.055	0.336	-0.136	0.062	0.028	-0.035	0.030	0.243	1.000	0.114	-0.044	0.033	0.180	1.000	**0.064**
7	rs11030104	0.033	0.057	0.561	0.025	0.044	0.566	0.015	0.041	0.720	0.032	0.045	0.479	0.025	0.023	0.275	1.000	0.991	0.023	0.025	0.349	1.000	0.960
8	rs11126666	0.073	0.062	0.236	0.005	0.047	0.922	-0.049	0.045	0.282	-0.045	0.050	0.361	-0.013	0.025	0.601	1.000	0.371	-0.030	0.027	0.273	1.000	0.670
9	rs11191560	0.056	0.067	0.402	-0.047	0.052	0.370	-0.018	0.046	0.693	-0.092	0.054	0.085	-0.032	0.027	0.228	1.000	0.364	-0.048	0.029	0.093	1.000	0.572
10	rs11583200	-0.012	0.097	0.905	-0.093	0.080	0.244	0.031	0.075	0.686	0.066	0.089	0.460	-0.004	0.042	0.930	1.000	0.557	-0.002	0.047	0.968	1.000	0.356
11	rs11688816	-0.055	0.060	0.359	-0.025	0.047	0.605	-0.013	0.046	0.773	0.009	0.050	0.850	-0.018	0.025	0.473	1.000	0.870	-0.010	0.028	0.712	1.000	0.882
12	rs12286929	0.042	0.064	0.511	-0.042	0.048	0.384	-0.124	0.049	0.011	-0.034	0.052	0.516	-0.049	0.026	0.060	1.000	0.214	-0.067	0.029	0.019	1.000	0.359
13	rs12429545	-0.009	0.071	0.904	0.034	0.048	0.480	-0.039	0.046	0.404	0.046	0.055	0.402	0.007	0.026	0.785	1.000	0.606	0.010	0.028	0.732	1.000	0.410
14	rs12566985	-0.052	0.081	0.524	0.055	0.056	0.326	-0.095	0.055	0.084	0.084	0.060	0.160	0.002	0.031	0.958	1.000	**0.096**	0.010	0.033	0.752	1.000	**0.054**
15	rs12940622	0.058	0.060	0.338	-0.016	0.047	0.728	0.015	0.045	0.743	-0.075	0.051	0.142	-0.008	0.025	0.747	1.000	0.362	-0.021	0.027	0.431	1.000	0.414
16	rs13021737	-0.085	0.093	0.359	0.027	0.087	0.760	0.009	0.075	0.907	0.016	0.088	0.859	-0.005	0.043	0.904	1.000	0.809	0.016	0.048	0.736	1.000	0.988
17	rs13201877	-0.287	0.198	0.148	-0.139	0.106	0.193	-0.081	0.104	0.436	0.366	0.121	0.003	-0.007	0.060	0.907	1.000	**0.004**	0.022	0.063	0.733	1.000	**0.003**
18	rs1441264	-0.036	0.058	0.531	0.021	0.045	0.641	0.057	0.042	0.176	-0.020	0.047	0.665	0.012	0.024	0.603	1.000	0.500	0.022	0.026	0.395	1.000	0.468
19	rs1460676	-0.030	0.062	0.630	0.020	0.047	0.674	0.013	0.042	0.765	0.075	0.047	0.111	0.024	0.024	0.310	1.000	0.570	0.034	0.026	0.191	1.000	0.576
20	rs1516725	0.045	0.099	0.652	0.033	0.087	0.700	0.137	0.079	0.084	0.085	0.087	0.327	0.080	0.044	0.066	1.000	0.816	0.088	0.048	0.068	1.000	0.677
21	rs1528435	-0.030	0.062	0.631	0.023	0.046	0.623	0.036	0.044	0.412	0.003	0.047	0.946	0.014	0.024	0.578	1.000	0.839	0.022	0.027	0.418	1.000	0.877
22	rs1558902	-0.051	0.089	0.569	1.45E-04	0.070	0.998	-0.050	0.067	0.453	0.110	0.077	0.154	0.001	0.037	0.976	1.000	0.404	0.012	0.041	0.768	1.000	0.285
23	rs16851483	-0.027	0.060	0.659	-0.068	0.050	0.169	0.035	0.048	0.468	0.005	0.051	0.922	-0.012	0.026	0.644	1.000	0.492	-0.009	0.029	0.763	1.000	0.311

Table 48 (continued): Interaction between 64 SNPs and calories intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	-0.005	0.062	0.941	-0.007	0.043	0.876	-0.029	0.043	0.495	0.011	0.047	0.810	-0.009	0.024	0.710	1.000	0.937	-0.009	0.025	0.710	1.000	0.814
25	rs17203016	0.173	0.088	0.049	0.009	0.062	0.888	0.061	0.061	0.318	-0.028	0.062	0.650	0.037	0.033	0.263	1.000	0.277	0.014	0.036	0.685	1.000	0.589
26	rs17405819	0.033	0.062	0.593	-0.045	0.045	0.314	-0.096	0.042	0.024	0.015	0.049	0.764	-0.036	0.024	0.140	1.000	0.226	-0.048	0.026	0.068	1.000	0.232
27	rs17724992	-0.043	0.056	0.443	0.094	0.045	0.035	-0.018	0.042	0.676	0.031	0.045	0.496	0.021	0.023	0.369	1.000	0.180	0.034	0.025	0.182	1.000	0.189
28	rs1928295	0.039	0.059	0.515	-0.097	0.045	0.033	0.020	0.041	0.630	-0.008	0.048	0.870	-0.015	0.024	0.513	1.000	0.186	-0.026	0.026	0.319	1.000	0.147
29	rs2033529	0.118	0.086	0.169	0.007	0.061	0.905	-0.072	0.055	0.192	0.029	0.060	0.630	0.002	0.032	0.938	1.000	0.279	-0.016	0.034	0.645	1.000	0.420
30	rs2033732	0.066	0.057	0.248	0.026	0.045	0.565	-0.022	0.043	0.619	-0.001	0.047	0.982	0.012	0.024	0.617	1.000	0.644	0.001	0.026	0.982	1.000	0.749
31	rs205262	-0.177	0.079	0.025	-0.043	0.060	0.474	0.106	0.060	0.077	0.095	0.066	0.151	0.011	0.032	0.729	1.000	**0.014**	0.05	0.036	0.161	1.000	0.153
32	rs2075650	0.155	0.106	0.146	0.020	0.075	0.790	-0.049	0.073	0.507	-0.061	0.078	0.431	-0.003	0.040	0.941	1.000	0.355	-0.029	0.043	0.499	1.000	0.714
33	rs2080454	0.024	0.060	0.683	0.033	0.044	0.455	-0.001	0.041	0.981	-0.040	0.044	0.359	0.001	0.023	0.954	1.000	0.668	-0.003	0.025	0.916	1.000	0.499
34	rs2112347	-0.092	0.056	0.100	-0.048	0.045	0.283	0.072	0.041	0.083	-0.013	0.045	0.767	-0.010	0.023	0.678	1.000	**0.079**	0.007	0.025	0.775	1.000	0.124
35	rs2176040	0.047	0.117	0.690	0.029	0.080	0.717	0.050	0.080	0.531	-0.111	0.087	0.201	0.002	0.044	0.962	1.000	0.509	-0.005	0.048	0.912	1.000	0.342
36	rs2207139	0.065	0.084	0.438	0.010	0.065	0.874	0.007	0.066	0.911	-0.071	0.064	0.270	-0.004	0.034	0.897	1.000	0.605	-0.018	0.038	0.625	1.000	0.601
37	rs2287019	0.138	0.067	0.040	0.024	0.056	0.670	0.052	0.056	0.349	-0.060	0.059	0.308	0.033	0.029	0.266	1.000	0.163	0.008	0.033	0.818	1.000	0.359
38	rs2365389	-0.020	0.085	0.810	0.015	0.066	0.820	0.071	0.066	0.283	-0.013	0.068	0.846	0.017	0.035	0.624	1.000	0.787	0.025	0.039	0.517	1.000	0.663
39	rs2820292	-0.028	0.071	0.699	-0.100	0.059	0.092	0.063	0.054	0.244	0.135	0.057	0.018	0.026	0.030	0.387	1.000	**0.027**	0.037	0.033	0.259	1.000	**0.014**
40	rs2836754	0.017	0.061	0.778	-0.007	0.043	0.871	0.040	0.041	0.337	-0.036	0.049	0.466	0.005	0.024	0.830	1.000	0.679	0.003	0.025	0.909	1.000	0.480
41	rs29941	-0.008	0.072	0.912	0.065	0.054	0.230	0.080	0.051	0.117	-0.152	0.060	0.011	0.007	0.029	0.808	1.000	**0.016**	0.010	0.032	0.754	1.000	**0.006**
42	rs3101336	0.036	0.104	0.728	-0.030	0.083	0.717	0.053	0.076	0.485	0.073	0.092	0.426	0.032	0.044	0.465	1.000	0.839	0.031	0.048	0.519	1.000	0.657
43	rs3817334	-0.008	0.061	0.901	-0.016	0.049	0.739	-0.003	0.047	0.944	-0.060	0.050	0.226	-0.023	0.025	0.376	1.000	0.845	-0.026	0.028	0.360	1.000	0.688
44	rs3849570	0.090	0.055	0.105	-0.007	0.046	0.878	0.013	0.043	0.764	-0.067	0.047	0.153	0.001	0.024	0.953	1.000	0.187	-0.018	0.026	0.485	1.000	0.434
45	rs3888190	0.124	0.114	0.276	0.029	0.081	0.716	0.067	0.076	0.379	-0.046	0.079	0.556	0.032	0.042	0.444	1.000	0.603	0.018	0.045	0.697	1.000	0.577
46	rs4256980	0.009	0.060	0.882	0.039	0.044	0.373	0.035	0.042	0.404	0.001	0.047	0.979	0.024	0.024	0.311	1.000	0.921	0.027	0.026	0.299	1.000	0.813

Table 48 (continued): Interaction between 64 SNPs and calories intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	-0.088	0.064	0.169	-0.013	0.053	0.799	0.011	0.047	0.823	0.032	0.054	0.551	-0.008	0.027	0.779	1.000	0.515	0.010	0.030	0.746	1.000	0.833
48	rs4787491	0.009	0.060	0.879	-0.052	0.043	0.228	0.044	0.041	0.276	-0.042	0.045	0.348	-0.010	0.023	0.657	1.000	0.341	-0.013	0.025	0.587	1.000	0.199
49	rs492400	0.071	0.071	0.317	0.034	0.054	0.527	-0.009	0.048	0.849	-0.009	0.053	0.862	0.014	0.027	0.611	1.000	0.751	0.004	0.030	0.894	1.000	0.799
50	rs6567160	-0.024	0.071	0.740	0.080	0.059	0.171	-0.010	0.055	0.854	0.077	0.063	0.224	0.032	0.031	0.290	1.000	0.496	0.045	0.034	0.184	1.000	0.444
51	rs6804842	-0.002	0.060	0.973	0.009	0.047	0.855	-0.067	0.045	0.137	0.036	0.046	0.429	-0.007	0.024	0.762	1.000	0.425	-0.008	0.027	0.752	1.000	0.249
52	rs7138803	0.047	0.072	0.512	0.010	0.050	0.847	-0.040	0.047	0.395	0.091	0.055	0.103	0.018	0.027	0.511	1.000	0.331	0.013	0.029	0.658	1.000	0.199
53	rs7141420	-0.076	0.056	0.179	0.004	0.045	0.927	-0.104	0.042	0.014	-0.054	0.047	0.254	-0.057	0.023	0.014	1.000	0.357	-0.053	0.026	0.038	1.000	0.212
54	rs7164727	-0.041	0.068	0.550	-0.040	0.050	0.428	0.023	0.049	0.641	0.039	0.054	0.463	-0.001	0.027	0.970	1.000	0.628	0.006	0.029	0.828	1.000	0.512
55	rs7239883	-0.008	0.061	0.895	0.032	0.047	0.503	-0.021	0.045	0.633	0.029	0.049	0.555	0.008	0.025	0.740	1.000	0.817	0.011	0.027	0.673	1.000	0.654
56	rs7243357	-0.008	0.070	0.910	0.050	0.052	0.331	-0.037	0.057	0.515	0.056	0.056	0.318	0.020	0.029	0.494	1.000	0.590	0.025	0.032	0.422	1.000	0.422
57	rs7599312	-0.133	0.230	0.561	0.147	0.160	0.357	-0.008	0.125	0.951	-0.025	0.181	0.889	0.013	0.081	0.872	1.000	0.757	0.034	0.087	0.696	1.000	0.698
58	rs7715256	0.169	0.160	0.292	0.066	0.121	0.585	-0.081	0.123	0.509	-0.019	0.115	0.872	0.017	0.063	0.783	1.000	0.616	-0.011	0.069	0.878	1.000	0.692
59	rs7903146	-0.177	0.207	0.394	-0.151	0.139	0.279	0.055	0.146	0.707	-0.323	0.189	0.088	-0.123	0.082	0.133	1.000	0.439	-0.113	0.089	0.205	1.000	0.269
60	rs9374842	-0.043	0.115	0.712	-0.054	0.072	0.453	-0.101	0.075	0.182	0.121	0.080	0.131	-0.021	0.041	0.608	1.000	0.212	-0.018	0.044	0.683	1.000	0.108
61	rs9400239	-0.023	0.062	0.706	-0.058	0.048	0.222	0.096	0.046	0.037	-0.012	0.052	0.818	0.006	0.025	0.820	1.000	0.112	0.012	0.028	0.675	1.000	**0.057**
62	rs9641123	0.033	0.061	0.595	-0.060	0.048	0.210	-0.031	0.046	0.498	0.030	0.048	0.527	-0.012	0.025	0.639	1.000	0.476	-0.020	0.027	0.453	1.000	0.392
63	rs977747	-0.099	0.141	0.483	0.097	0.111	0.381	0.140	0.108	0.193	-0.033	0.097	0.735	0.036	0.056	0.523	1.000	0.447	0.060	0.060	0.320	1.000	0.452
64	rs9914578	0.064	0.066	0.329	-0.013	0.054	0.805	-0.096	0.053	0.073	-0.030	0.060	0.614	-0.027	0.029	0.357	1.000	0.302	-0.048	0.032	0.133	1.000	0.524

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions (P_{adjust} < 0 .05) and heterogeneity (Q_{pvalue} < 0.1) findings are in bold.

Table 49: Interaction between 64 SNPs and cholesterol intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	-0.129	0.064	0.043	-0.111	0.046	0.015	0.006	0.042	0.878	-0.036	0.048	0.452	-0.056	0.024	0.020	1.000	0.158	-0.044	0.026	0.091	1.000	0.161
2	rs1016287	0.071	0.064	0.266	-0.041	0.050	0.413	-0.040	0.052	0.438	0.055	0.052	0.288	0.005	0.027	0.863	1.000	0.307	-0.010	0.030	0.747	1.000	0.317
3	rs10182181	0.035	0.057	0.536	0.050	0.045	0.269	-0.055	0.042	0.187	-0.052	0.046	0.257	-0.011	0.023	0.630	1.000	0.221	-0.021	0.026	0.419	1.000	0.166
4	rs10733682	-0.009	0.072	0.905	-0.006	0.054	0.907	-0.073	0.048	0.129	-0.015	0.056	0.792	-0.031	0.028	0.264	1.000	0.764	-0.035	0.030	0.246	1.000	0.594
5	rs10938397	0.142	0.065	0.031	0.055	0.049	0.267	-0.041	0.047	0.381	-0.070	0.053	0.187	0.008	0.026	0.749	1.000	**0.039**	-0.017	0.029	0.549	1.000	0.184
6	rs10968576	-0.046	0.074	0.539	-0.001	0.058	0.984	-0.096	0.058	0.097	-0.082	0.064	0.207	-0.056	0.031	0.074	1.000	0.672	-0.058	0.035	0.092	1.000	0.468
7	rs11030104	-0.031	0.057	0.584	-0.027	0.041	0.509	-0.039	0.041	0.342	0.025	0.045	0.587	-0.019	0.022	0.406	1.000	0.742	-0.016	0.024	0.503	1.000	0.553
8	rs11126666	-0.105	0.058	0.071	-0.010	0.046	0.835	-0.002	0.045	0.960	-0.025	0.051	0.619	-0.028	0.025	0.252	1.000	0.523	-0.011	0.027	0.675	1.000	0.943
9	rs11191560	-0.040	0.067	0.550	0.047	0.053	0.371	-0.020	0.044	0.646	-0.027	0.054	0.623	-0.008	0.026	0.764	1.000	0.677	-0.002	0.029	0.945	1.000	0.535
10	rs11583200	0.164	0.093	0.077	0.003	0.083	0.974	0.027	0.081	0.743	0.132	0.092	0.153	0.074	0.043	0.090	1.000	0.491	0.048	0.049	0.327	1.000	0.551
11	rs11688816	0.161	0.062	0.009	-0.003	0.047	0.943	0.005	0.045	0.913	0.013	0.051	0.801	0.030	0.025	0.225	1.000	0.140	0.004	0.027	0.873	1.000	0.973
12	rs12286929	0.087	0.067	0.193	-0.013	0.050	0.799	0.026	0.049	0.594	-0.108	0.052	0.038	-0.010	0.026	0.697	1.000	0.101	-0.029	0.029	0.323	1.000	0.157
13	rs12429545	0.008	0.068	0.908	0.019	0.049	0.699	-0.048	0.049	0.326	0.076	0.055	0.165	0.011	0.027	0.691	1.000	0.408	0.011	0.029	0.702	1.000	0.235
14	rs12566985	0.014	0.073	0.845	0.078	0.057	0.173	0.042	0.055	0.446	0.004	0.059	0.950	0.037	0.030	0.214	1.000	0.816	0.042	0.033	0.202	1.000	0.665
15	rs12940622	-0.159	0.062	0.011	0.002	0.048	0.970	-0.081	0.046	0.076	0.021	0.050	0.680	-0.045	0.025	0.073	1.000	**0.084**	-0.023	0.028	0.407	1.000	0.266
16	rs13021737	-0.067	0.116	0.563	-0.098	0.088	0.269	0.104	0.075	0.168	0.107	0.088	0.224	0.029	0.044	0.515	1.000	0.211	0.045	0.048	0.346	1.000	0.156
17	rs13201877	-0.225	0.176	0.201	0.104	0.103	0.314	0.171	0.109	0.118	-0.104	0.122	0.398	0.036	0.060	0.551	1.000	0.141	0.070	0.064	0.271	1.000	0.227
18	rs1441264	0.064	0.058	0.276	-0.030	0.044	0.486	-0.018	0.044	0.679	0.009	0.047	0.854	-0.002	0.024	0.946	1.000	0.599	-0.014	0.026	0.578	1.000	0.826
19	rs1460676	0.006	0.061	0.922	-0.010	0.045	0.827	0.066	0.042	0.112	0.003	0.045	0.951	0.020	0.023	0.393	1.000	0.602	0.022	0.025	0.377	1.000	0.407
20	rs1516725	-0.078	0.109	0.472	-0.069	0.081	0.395	0.247	0.082	0.003	0.091	0.086	0.292	0.061	0.044	0.161	1.000	**0.023**	0.089	0.048	0.065	1.000	**0.023**
21	rs1528435	4.74E-04	0.063	0.994	-0.035	0.045	0.437	-0.040	0.045	0.377	0.014	0.048	0.767	-0.018	0.024	0.454	1.000	0.822	-0.022	0.027	0.415	1.000	0.667
22	rs1558902	-0.011	0.083	0.891	0.002	0.063	0.976	0.136	0.067	0.042	0.120	0.080	0.136	0.062	0.036	0.085	1.000	0.328	0.079	0.040	0.048	1.000	0.289
23	rs16851483	0.067	0.066	0.308	0.037	0.051	0.470	-0.028	0.047	0.551	-0.041	0.057	0.474	0.003	0.027	0.908	1.000	0.490	-0.010	0.030	0.740	1.000	0.527

Table 49 (continued): Interaction between 64 SNPs and cholesterol intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	0.071	0.057	0.209	-0.067	0.042	0.110	-0.046	0.043	0.279	0.035	0.048	0.462	-0.014	0.023	0.550	1.000	0.139	-0.031	0.025	0.222	1.000	0.249
25	rs17203016	-0.040	0.092	0.667	-0.090	0.062	0.146	-0.106	0.062	0.085	0.071	0.070	0.308	-0.049	0.034	0.151	1.000	0.234	-0.051	0.037	0.170	1.000	0.119
26	rs17405819	-0.046	0.058	0.427	-0.049	0.046	0.292	0.054	0.042	0.196	0.040	0.046	0.384	0.008	0.024	0.747	1.000	0.254	0.018	0.026	0.482	1.000	0.217
27	rs17724992	-0.055	0.057	0.342	-0.062	0.042	0.144	0.022	0.041	0.581	0.004	0.045	0.930	-0.018	0.023	0.422	1.000	0.439	-0.011	0.025	0.640	1.000	0.328
28	rs1928295	-0.062	0.061	0.315	0.061	0.045	0.169	0.030	0.042	0.473	0.033	0.046	0.467	0.026	0.023	0.264	1.000	0.439	0.041	0.025	0.105	1.000	0.857
29	rs2033529	-0.088	0.087	0.312	-0.081	0.061	0.184	-0.053	0.056	0.348	-0.152	0.062	0.014	-0.092	0.032	0.004	0.296	0.684	-0.093	0.034	0.007	0.516	0.475
30	rs2033732	0.026	0.058	0.657	0.004	0.046	0.925	0.049	0.044	0.269	-0.032	0.046	0.488	0.011	0.024	0.642	1.000	0.639	0.008	0.026	0.756	1.000	0.446
31	rs205262	-0.085	0.079	0.282	0.206	0.065	0.002	0.065	0.060	0.274	0.082	0.068	0.230	0.080	0.033	0.017	1.000	0.042	0.116	0.037	0.002	0.124	0.236
32	rs2075650	0.201	0.108	0.065	0.013	0.088	0.884	-0.070	0.079	0.374	0.120	0.089	0.179	0.045	0.045	0.311	1.000	0.170	0.013	0.049	0.787	1.000	0.280
33	rs2080454	-1.30E-04	0.059	0.998	-0.012	0.043	0.788	-0.010	0.040	0.797	0.044	0.046	0.340	0.004	0.023	0.852	1.000	0.797	0.005	0.025	0.839	1.000	0.604
34	rs2112347	0.066	0.057	0.244	-0.007	0.046	0.878	-0.111	0.043	0.010	-0.034	0.047	0.472	-0.033	0.024	0.164	1.000	**0.082**	-0.054	0.026	0.039	1.000	0.223
35	rs2176040	0.029	0.121	0.814	-0.125	0.088	0.155	-0.024	0.079	0.764	0.003	0.087	0.973	-0.036	0.045	0.427	1.000	0.674	-0.046	0.049	0.342	1.000	0.546
36	rs2207139	0.028	0.084	0.734	-0.059	0.067	0.385	0.086	0.063	0.171	-0.062	0.062	0.323	-0.003	0.034	0.923	1.000	0.294	-0.009	0.037	0.799	1.000	0.170
37	rs2287019	0.165	0.077	0.032	0.092	0.052	0.078	-0.039	0.055	0.478	-0.024	0.059	0.692	0.037	0.030	0.210	1.000	**0.077**	0.015	0.032	0.647	1.000	0.169
38	rs2365389	0.115	0.080	0.152	-0.039	0.061	0.519	0.053	0.064	0.407	-0.069	0.070	0.328	0.007	0.034	0.834	1.000	0.254	-0.016	0.037	0.664	1.000	0.393
39	rs2820292	0.094	0.066	0.154	-0.023	0.060	0.694	0.026	0.054	0.633	-0.080	0.056	0.156	-0.001	0.029	0.968	1.000	0.218	-0.025	0.033	0.452	1.000	0.399
40	rs2836754	-0.098	0.058	0.092	-0.012	0.047	0.798	-0.086	0.042	0.043	-0.019	0.049	0.695	-0.052	0.024	0.030	1.000	0.479	-0.043	0.026	0.106	1.000	0.423
41	rs29941	0.072	0.074	0.329	0.073	0.052	0.158	-0.040	0.051	0.426	0.042	0.056	0.459	0.030	0.028	0.284	1.000	0.394	0.023	0.030	0.449	1.000	0.271
42	rs3101336	-0.088	0.113	0.440	-0.164	0.079	0.037	-0.126	0.071	0.077	0.054	0.091	0.549	-0.092	0.042	0.029	1.000	0.299	-0.093	0.046	0.041	1.000	0.159
43	rs3817334	0.048	0.062	0.432	-0.012	0.047	0.792	-0.008	0.048	0.873	-0.108	0.051	0.034	-0.024	0.025	0.338	1.000	0.233	-0.039	0.028	0.159	1.000	0.273
44	rs3849570	0.043	0.059	0.464	0.014	0.045	0.756	-0.008	0.040	0.851	-0.049	0.046	0.290	-0.005	0.023	0.845	1.000	0.626	-0.013	0.025	0.602	1.000	0.612
45	rs3888190	-0.108	0.110	0.326	-0.056	0.093	0.548	0.100	0.077	0.193	0.039	0.078	0.621	0.015	0.043	0.735	1.000	0.368	0.037	0.047	0.429	1.000	0.433
46	rs4256980	0.012	0.064	0.854	-0.017	0.044	0.702	0.043	0.043	0.311	-0.078	0.045	0.079	-0.012	0.023	0.613	1.000	0.257	-0.016	0.025	0.537	1.000	0.144

Table 49 (continued): Interaction between 64 SNPs and cholesterol intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	0.087	0.066	0.186	0.109	0.053	0.039	0.077	0.049	0.119	0.103	0.056	0.064	0.094	0.027	**6.40E-04**	**0.047**	0.971	0.095	0.030	0.002	0.121	0.893
48	rs4787491	-0.017	0.058	0.770	0.034	0.043	0.420	0.024	0.041	0.554	-0.043	0.046	0.349	0.004	0.023	0.861	1.000	0.587	0.008	0.025	0.752	1.000	0.411
49	rs492400	0.018	0.074	0.807	0.118	0.056	0.035	0.007	0.051	0.892	-0.048	0.052	0.356	0.021	0.028	0.462	1.000	0.182	0.021	0.030	0.487	1.000	**0.088**
50	rs6567160	-0.010	0.076	0.891	-0.018	0.061	0.762	-0.051	0.055	0.353	-0.124	0.062	0.046	-0.054	0.031	0.082	1.000	0.584	-0.063	0.034	0.065	1.000	0.461
51	rs6804842	0.043	0.062	0.485	-0.037	0.047	0.433	0.039	0.045	0.388	0.015	0.048	0.759	0.012	0.025	0.616	1.000	0.639	0.007	0.027	0.809	1.000	0.497
52	rs7138803	0.072	0.072	0.313	-0.006	0.050	0.900	0.052	0.046	0.261	0.068	0.055	0.219	0.042	0.027	0.120	1.000	0.708	0.037	0.029	0.203	1.000	0.556
53	rs7141420	0.174	0.059	0.004	-0.002	0.045	0.959	-0.032	0.042	0.455	-0.018	0.044	0.678	0.011	0.023	0.625	1.000	**0.029**	-0.018	0.025	0.477	1.000	0.892
54	rs7164727	-0.082	0.070	0.243	0.036	0.050	0.476	-0.034	0.049	0.491	-0.024	0.049	0.632	-0.018	0.026	0.486	1.000	0.553	-0.008	0.029	0.783	1.000	0.566
55	rs7239883	-0.032	0.065	0.621	-0.026	0.048	0.593	-0.018	0.043	0.683	-0.065	0.050	0.193	-0.034	0.025	0.175	1.000	0.907	-0.034	0.027	0.207	1.000	0.758
56	rs7243357	-0.156	0.073	0.033	0.025	0.050	0.611	0.086	0.057	0.134	-0.045	0.056	0.426	-0.006	0.029	0.838	1.000	**0.053**	0.022	0.031	0.486	1.000	0.265
57	rs7599312	0.105	0.249	0.672	-0.166	0.176	0.345	-0.162	0.122	0.184	-0.119	0.161	0.458	-0.124	0.080	0.122	1.000	0.800	-0.151	0.085	0.076	1.000	0.973
58	rs7715256	0.245	0.173	0.158	0.059	0.138	0.667	-0.049	0.113	0.662	-0.215	0.124	0.084	-0.029	0.066	0.666	1.000	0.159	-0.075	0.072	0.293	1.000	0.322
59	rs7903146	-0.206	0.219	0.346	-0.030	0.119	0.801	-0.225	0.195	0.249	0.042	0.136	0.755	-0.058	0.076	0.443	1.000	0.616	-0.038	0.081	0.641	1.000	0.529
60	rs9374842	-0.295	0.124	0.018	0.027	0.078	0.728	-0.032	0.072	0.659	-0.070	0.082	0.389	-0.054	0.042	0.192	1.000	0.175	-0.024	0.044	0.588	1.000	0.682
61	rs9400239	0.146	0.065	0.025	0.024	0.047	0.602	-0.066	0.046	0.155	-0.081	0.052	0.123	-0.010	0.026	0.709	1.000	**0.023**	-0.038	0.028	0.173	1.000	0.245
62	rs9641123	-0.061	0.065	0.349	0.030	0.048	0.529	-0.016	0.044	0.721	0.038	0.049	0.441	0.004	0.025	0.880	1.000	0.577	0.015	0.027	0.579	1.000	0.667
63	rs977747	0.020	0.176	0.912	0.190	0.109	0.081	-0.084	0.109	0.441	0.036	0.100	0.721	0.044	0.058	0.446	1.000	0.361	0.047	0.061	0.442	1.000	0.203
64	rs9914578	0.032	0.069	0.638	0.067	0.054	0.219	0.065	0.053	0.214	-0.126	0.059	0.032	0.014	0.029	0.635	1.000	**0.053**	0.010	0.032	0.761	1.000	**0.022**

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions (P_{adjust} < 0 .05) and heterogeneity (Q_{pvalue} < 0.1) findings are in bold.

As can be seen, the minor risk allele T would decrease the BMI level in the individuals in the lower cholesterol intake group while increased BMI level in the higher cholesterol intake group.

6.3.7.3 Starch

Table 50 shows the interaction results between 64 SNPs and starch intake on Z-BMI. None of the interaction remained statistically significant after adjusting for multiple testing. Nominal significant positive SNP × starch interaction on BMI was observed for *KCNK3* rs11126666 (β=0.059, SE=0.025, $P_{interaction}$=0.017), *CREB1* rs17203016 (β=0.065, SE=0.033, $P_{interaction}$= 0.045), *INO80E* rs4787491 (β=0.055, SE=0.023, $P_{interaction}$= 0.016) and *LOC646736* rs2176040 (β=0.105, SE=0.047, $P_{interaction}$= 0.024). The BMI level increased as the number of reported BMI risk alleles and the intake of starch increased.

6.3.7.4 Fiber

Table 51 shows the interaction results between 64 SNPs and fiber intake on Z-BMI. None of the interaction remained statistically significant after adjusting for multiple testing. Nominal significant SNP × fiber interaction on BMI was observed for *IFNGR1* rs13201877 (β=-0.132, SE=0.063, $P_{interaction}$=0.038) and *MC4R* rs6567160 (β=0.068, SE=0.032, $P_{interaction}$= 0.032). In the case of rs13201877, BMI level decreased as the number of G allele and the intake of fiber increased while for rs6567160, BMI level increased as the number of C allele and fiber intake increased.

Table 50: Interaction between 64 SNPs and starch intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	0.090	0.062	0.147	0.018	0.045	0.693	-0.057	0.043	0.185	0.077	0.047	0.104	0.020	0.024	0.392	1.000	0.115	0.008	0.026	0.749	1.000	0.107
2	rs1016287	-0.047	0.066	0.478	0.025	0.050	0.626	0.126	0.049	0.011	-0.009	0.053	0.862	0.034	0.027	0.201	1.000	0.129	0.050	0.029	0.086	1.000	0.146
3	rs10182181	-0.061	0.059	0.307	-0.069	0.044	0.118	0.025	0.044	0.560	0.002	0.044	0.965	-0.021	0.023	0.373	1.000	0.385	-0.014	0.025	0.595	1.000	0.286
4	rs10733682	0.172	0.069	0.013	0.027	0.052	0.601	0.023	0.046	0.621	0.027	0.056	0.629	0.048	0.027	0.076	1.000	0.282	0.025	0.029	0.387	1.000	0.997
5	rs10938397	-0.012	0.064	0.855	0.031	0.051	0.543	-0.001	0.047	0.980	1.69E-04	0.053	0.997	0.006	0.026	0.821	1.000	0.950	0.010	0.029	0.740	1.000	0.878
6	rs10968576	0.063	0.075	0.406	0.048	0.058	0.409	-0.016	0.056	0.773	0.063	0.054	0.242	0.037	0.030	0.215	1.000	0.732	0.032	0.032	0.321	1.000	0.563
7	rs11030104	0.019	0.056	0.736	0.010	0.043	0.812	-0.004	0.041	0.928	0.113	0.045	0.013	0.033	0.023	0.144	1.000	0.232	0.036	0.025	0.147	1.000	0.122
8	rs11126666	0.041	0.060	0.497	0.012	0.047	0.805	0.042	0.047	0.368	0.142	0.048	0.004	0.059	0.025	0.017	1.000	0.245	0.063	0.027	0.021	1.000	0.132
9	rs11191560	-0.023	0.068	0.731	-0.063	0.050	0.204	-0.048	0.046	0.293	-0.047	0.053	0.377	-0.048	0.026	0.065	1.000	0.973	-0.053	0.028	0.064	1.000	0.967
10	rs11583200	-0.085	0.092	0.354	0.038	0.079	0.631	-0.079	0.074	0.281	-0.004	0.095	0.966	-0.033	0.042	0.424	1.000	0.655	-0.020	0.047	0.672	1.000	0.544
11	rs11688816	-0.015	0.061	0.803	0.044	0.048	0.356	-0.042	0.047	0.372	0.017	0.052	0.738	0.002	0.025	0.947	1.000	0.611	0.005	0.028	0.851	1.000	0.422
12	rs12286929	0.065	0.068	0.336	-0.046	0.047	0.333	0.015	0.049	0.769	0.010	0.052	0.849	0.002	0.026	0.928	1.000	0.577	-0.009	0.029	0.758	1.000	0.617
13	rs12429545	0.039	0.071	0.585	-0.067	0.049	0.172	-0.028	0.049	0.565	-0.071	0.054	0.188	-0.041	0.027	0.128	1.000	0.590	-0.054	0.029	0.062	1.000	0.799
14	rs12566985	0.078	0.074	0.290	-0.063	0.055	0.258	-0.033	0.056	0.551	0.035	0.064	0.584	-0.008	0.030	0.802	1.000	0.392	-0.025	0.033	0.450	1.000	0.505
15	rs12940622	0.036	0.060	0.556	0.084	0.046	0.067	0.006	0.044	0.883	0.006	0.050	0.908	0.033	0.024	0.175	1.000	0.594	0.033	0.027	0.222	1.000	0.387
16	rs13021737	0.189	0.107	0.077	0.019	0.090	0.833	0.028	0.076	0.717	0.013	0.098	0.892	0.051	0.045	0.257	1.000	0.565	0.021	0.050	0.671	1.000	0.993
17	rs13201877	-0.114	0.157	0.469	0.082	0.104	0.430	-0.149	0.105	0.154	0.142	0.112	0.205	0.003	0.057	0.965	1.000	0.188	0.020	0.062	0.740	1.000	0.125
18	rs1441264	0.023	0.059	0.693	0.033	0.046	0.475	-0.069	0.042	0.105	0.015	0.046	0.736	-0.005	0.024	0.836	1.000	0.338	-0.010	0.026	0.690	1.000	0.213
19	rs1460676	-0.019	0.060	0.757	0.006	0.048	0.901	-0.021	0.041	0.601	0.037	0.046	0.427	0.001	0.024	0.967	1.000	0.798	0.005	0.026	0.860	1.000	0.641
20	rs1516725	0.117	0.100	0.244	0.102	0.080	0.200	-0.097	0.072	0.179	-0.057	0.090	0.531	0.004	0.042	0.924	1.000	0.158	-0.020	0.046	0.666	1.000	0.160
21	rs1528435	0.037	0.061	0.539	-0.001	0.047	0.984	-0.057	0.045	0.210	0.004	0.048	0.940	-0.010	0.025	0.685	1.000	0.617	-0.019	0.027	0.474	1.000	0.587
22	rs1558902	0.021	0.085	0.810	-0.026	0.064	0.687	0.024	0.065	0.710	0.139	0.072	0.054	0.036	0.035	0.307	1.000	0.384	0.039	0.039	0.311	1.000	0.222
23	rs16851483	0.022	0.070	0.750	0.008	0.052	0.882	0.003	0.048	0.956	0.054	0.054	0.318	0.020	0.027	0.461	1.000	0.901	0.020	0.030	0.506	1.000	0.748

Table 50 (continued): Interaction between 64 SNPs and starch intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	0.029	0.058	0.615	0.024	0.042	0.569	0.016	0.043	0.705	-0.026	0.047	0.577	0.010	0.023	0.655	1.000	0.841	0.007	0.025	0.788	1.000	0.702
25	rs17203016	0.126	0.085	0.139	0.030	0.059	0.610	0.045	0.059	0.446	0.099	0.066	0.135	0.065	0.033	0.045	1.000	0.745	0.055	0.035	0.119	1.000	0.726
26	rs17405819	0.085	0.059	0.152	0.041	0.046	0.379	0.012	0.042	0.771	-0.027	0.046	0.549	0.021	0.024	0.382	1.000	0.472	0.008	0.026	0.741	1.000	0.574
27	rs17724992	0.056	0.060	0.351	0.019	0.043	0.665	0.012	0.040	0.758	-0.049	0.046	0.288	0.005	0.023	0.814	1.000	0.526	-0.003	0.025	0.894	1.000	0.497
28	rs1928295	-0.036	0.060	0.552	-0.053	0.044	0.234	0.051	0.043	0.234	0.036	0.048	0.450	0.004	0.024	0.868	1.000	0.292	0.011	0.026	0.661	1.000	0.201
29	rs2033529	0.140	0.079	0.077	0.018	0.061	0.771	-0.036	0.052	0.481	0.009	0.062	0.880	0.015	0.031	0.629	1.000	0.321	-0.007	0.033	0.829	1.000	0.756
30	rs2033732	-0.027	0.059	0.649	0.106	0.047	0.023	0.005	0.043	0.908	0.073	0.045	0.100	0.045	0.024	0.056	1.000	0.215	0.059	0.026	0.023	1.000	0.258
31	rs205262	-0.012	0.079	0.878	-0.067	0.063	0.291	-0.036	0.060	0.554	-0.074	0.072	0.302	-0.049	0.034	0.148	1.000	0.927	-0.057	0.037	0.127	1.000	0.903
32	rs2075650	0.052	0.113	0.646	-0.081	0.082	0.326	0.050	0.071	0.484	0.002	0.087	0.986	0.004	0.042	0.927	1.000	0.646	-0.004	0.046	0.931	1.000	0.485
33	rs2080454	-0.026	0.061	0.670	0.040	0.044	0.353	0.040	0.041	0.330	-0.035	0.045	0.437	0.011	0.023	0.634	1.000	0.499	0.017	0.025	0.493	1.000	0.378
34	rs2112347	-0.017	0.059	0.769	0.010	0.047	0.832	0.012	0.042	0.778	0.056	0.045	0.209	0.019	0.023	0.419	1.000	0.768	0.026	0.025	0.314	1.000	0.708
35	rs2176040	0.192	0.114	0.092	-0.008	0.088	0.929	0.155	0.085	0.069	0.114	0.093	0.222	0.105	0.047	0.024	1.000	0.460	0.088	0.051	0.086	1.000	0.389
36	rs2207139	0.027	0.084	0.748	0.074	0.066	0.264	0.011	0.068	0.871	-0.004	0.067	0.948	0.027	0.035	0.436	1.000	0.855	0.027	0.039	0.478	1.000	0.678
37	rs2287019	-0.079	0.075	0.289	-0.087	0.054	0.109	0.017	0.052	0.740	-0.043	0.062	0.483	-0.043	0.030	0.149	1.000	0.528	-0.036	0.032	0.265	1.000	0.381
38	rs2365389	-0.094	0.087	0.281	0.037	0.059	0.534	0.009	0.067	0.896	0.024	0.074	0.743	0.005	0.035	0.875	1.000	0.648	0.024	0.038	0.521	1.000	0.952
39	rs2820292	-0.087	0.070	0.217	-0.021	0.061	0.733	0.02	0.052	0.705	0.096	0.058	0.098	0.011	0.030	0.704	1.000	0.222	0.032	0.033	0.323	1.000	0.363
40	rs2836754	0.026	0.058	0.655	-0.004	0.046	0.931	0.019	0.042	0.655	-0.027	0.049	0.580	0.003	0.024	0.903	1.000	0.874	-0.002	0.026	0.947	1.000	0.775
41	rs29941	-0.250	0.078	0.001	-0.035	0.050	0.481	0.032	0.050	0.519	0.024	0.057	0.673	-0.028	0.028	0.326	1.000	**0.016**	0.006	0.030	0.853	1.000	0.590
42	rs3101336	0.054	0.107	0.617	0.066	0.083	0.431	0.087	0.079	0.269	-0.060	0.090	0.506	0.040	0.044	0.361	1.000	0.636	0.037	0.048	0.437	1.000	0.431
43	rs3817334	-0.023	0.061	0.700	-0.017	0.049	0.726	0.087	0.046	0.059	-0.001	0.052	0.985	0.018	0.025	0.492	1.000	0.338	0.026	0.028	0.349	1.000	0.244
44	rs3849570	0.028	0.057	0.627	0.034	0.042	0.425	-2.60E-04	0.041	0.995	0.067	0.048	0.161	0.030	0.023	0.193	1.000	0.765	0.030	0.025	0.227	1.000	0.563
45	rs3888190	0.006	0.104	0.958	-0.049	0.079	0.530	0.004	0.078	0.956	0.021	0.080	0.794	-0.006	0.042	0.884	1.000	0.930	-0.008	0.046	0.855	1.000	0.806
46	rs4256980	-0.018	0.064	0.772	-0.063	0.044	0.153	-0.053	0.042	0.209	0.012	0.046	0.801	-0.034	0.024	0.147	1.000	0.643	-0.037	0.026	0.148	1.000	0.449

Table 50 (continued): Interaction between 64 SNPs and starch intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	-0.069	0.067	0.302	-0.024	0.053	0.654	0.003	0.048	0.958	-0.044	0.054	0.417	-0.028	0.027	0.302	1.000	0.834	-0.020	0.030	0.504	1.000	0.812
48	rs4787491	0.134	0.059	0.025	0.032	0.042	0.456	0.004	0.041	0.924	0.101	0.046	0.029	0.055	0.023	0.016	1.000	0.207	0.042	0.025	0.093	1.000	0.282
49	rs492400	0.012	0.077	0.874	-0.011	0.052	0.840	-0.013	0.049	0.790	-0.033	0.053	0.531	-0.015	0.028	0.597	1.000	0.969	-0.019	0.030	0.530	1.000	0.946
50	rs6567160	-0.004	0.078	0.958	0.024	0.059	0.686	0.027	0.056	0.625	0.040	0.065	0.538	0.024	0.031	0.441	1.000	0.979	0.030	0.034	0.388	1.000	0.982
51	rs6804842	-0.028	0.062	0.650	0.004	0.048	0.938	0.060	0.048	0.210	0.020	0.046	0.661	0.019	0.025	0.453	1.000	0.702	0.028	0.027	0.309	1.000	0.692
52	rs7138803	-0.007	0.069	0.914	-0.087	0.051	0.091	0.068	0.046	0.139	-0.034	0.055	0.539	-0.009	0.027	0.724	1.000	0.150	-0.010	0.029	0.735	1.000	**0.070**
53	rs7141420	0.006	0.058	0.920	-0.016	0.043	0.718	-0.003	0.042	0.934	0.017	0.046	0.718	-4.20E-04	0.023	0.986	1.000	0.964	-0.002	0.025	0.949	1.000	0.876
54	rs7164727	0.060	0.071	0.392	0.007	0.051	0.889	-0.025	0.048	0.598	-0.060	0.053	0.258	-0.013	0.027	0.635	1.000	0.555	-0.025	0.029	0.385	1.000	0.663
55	rs7239883	-0.032	0.064	0.613	0.005	0.046	0.917	-0.047	0.044	0.284	0.024	0.050	0.631	-0.013	0.025	0.612	1.000	0.708	-0.009	0.027	0.736	1.000	0.528
56	rs7243357	0.132	0.067	0.049	0.021	0.054	0.696	-0.020	0.057	0.719	0.077	0.059	0.192	0.045	0.029	0.124	1.000	0.320	0.024	0.032	0.453	1.000	0.492
57	rs7599312	-0.197	0.194	0.312	-0.016	0.143	0.911	-0.185	0.127	0.147	0.032	0.162	0.841	-0.092	0.076	0.222	1.000	0.638	-0.074	0.082	0.369	1.000	0.508
58	rs7715256	-0.113	0.155	0.465	-0.162	0.160	0.310	0.092	0.107	0.390	0.027	0.126	0.832	-0.006	0.066	0.926	1.000	0.504	0.018	0.073	0.810	1.000	0.415
59	rs7903146	0.232	0.226	0.306	-0.016	0.114	0.889	-0.180	0.143	0.208	0.082	0.162	0.612	-0.013	0.074	0.860	1.000	0.410	-0.042	0.078	0.589	1.000	0.456
60	rs9374842	0.084	0.124	0.496	0.047	0.078	0.546	-0.089	0.072	0.217	0.036	0.082	0.659	0.002	0.042	0.954	1.000	0.467	-0.008	0.044	0.855	1.000	0.358
61	rs9400239	0.040	0.063	0.528	0.020	0.048	0.680	-0.069	0.045	0.128	-0.077	0.050	0.122	-0.029	0.025	0.248	1.000	0.267	-0.042	0.027	0.125	1.000	0.283
62	rs9641123	0.049	0.061	0.428	-0.039	0.046	0.400	0.024	0.043	0.575	-0.005	0.049	0.921	0.003	0.024	0.889	1.000	0.650	-0.005	0.026	0.850	1.000	0.607
63	rs977747	0.269	0.163	0.098	-0.164	0.126	0.192	0.023	0.123	0.852	-0.083	0.107	0.440	-0.023	0.063	0.711	1.000	0.176	-0.074	0.068	0.275	1.000	0.565
64	rs9914578	-0.054	0.075	0.468	-0.028	0.055	0.618	-0.032	0.053	0.547	0.043	0.058	0.453	-0.015	0.029	0.615	1.000	0.693	-0.008	0.032	0.813	1.000	0.571

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions (P_{adjust} < 0 .05) and heterogeneity (Q_{pvalue} < 0.1) findings are in bold.

Table 51: Interaction between 64 SNPs and fiber intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	-0.058	0.063	0.357	-0.004	0.044	0.921	-0.067	0.041	0.106	0.057	0.048	0.231	-0.017	0.024	0.464	1.000	0.223	-0.011	0.026	0.677	1.000	0.143
2	rs1016287	0.045	0.066	0.497	-0.026	0.049	0.589	0.079	0.050	0.117	0.078	0.054	0.147	0.041	0.027	0.123	1.000	0.401	0.041	0.029	0.165	1.000	0.230
3	rs10182181	0.084	0.059	0.151	-0.091	0.044	0.040	0.041	0.042	0.331	0.036	0.046	0.427	0.010	0.023	0.663	1.000	**0.054**	-0.004	0.025	0.880	1.000	**0.056**
4	rs10733682	-0.137	0.069	0.046	0.024	0.053	0.650	-0.047	0.049	0.340	-0.024	0.059	0.688	-0.037	0.028	0.188	1.000	0.317	-0.017	0.031	0.583	1.000	0.614
5	rs10938397	-0.147	0.068	0.030	-0.021	0.050	0.678	0.086	0.048	0.076	0.037	0.050	0.465	0.008	0.026	0.769	1.000	**0.036**	0.035	0.029	0.215	1.000	0.311
6	rs10968576	0.028	0.077	0.719	0.018	0.062	0.767	0.005	0.054	0.919	0.053	0.058	0.361	0.025	0.031	0.408	1.000	0.945	0.025	0.033	0.455	1.000	0.828
7	rs11030104	-0.031	0.056	0.585	0.043	0.042	0.310	-0.030	0.043	0.477	-0.018	0.045	0.685	-0.006	0.023	0.796	1.000	0.586	-0.001	0.025	0.967	1.000	0.427
8	rs11126666	-0.085	0.061	0.165	-0.009	0.049	0.852	0.052	0.046	0.267	0.044	0.048	0.352	0.011	0.025	0.669	1.000	0.274	0.030	0.027	0.276	1.000	0.623
9	rs11191560	-0.032	0.068	0.636	0.035	0.051	0.497	0.007	0.046	0.877	0.082	0.052	0.115	0.028	0.026	0.289	1.000	0.557	0.039	0.029	0.178	1.000	0.560
10	rs11583200	0.009	0.099	0.928	0.005	0.079	0.950	-0.022	0.080	0.779	-0.073	0.091	0.421	-0.020	0.043	0.646	1.000	0.913	-0.026	0.048	0.581	1.000	0.809
11	rs11688816	-0.067	0.060	0.263	-0.119	0.048	0.012	0.051	0.045	0.252	-0.050	0.049	0.302	-0.041	0.025	0.098	1.000	**0.066**	-0.035	0.027	0.191	1.000	**0.031**
12	rs12286929	-0.139	0.069	0.044	0.032	0.047	0.497	-0.050	0.048	0.302	0.034	0.049	0.490	-0.015	0.026	0.571	1.000	0.125	0.006	0.028	0.841	1.000	0.375
13	rs12429545	0.032	0.069	0.642	0.020	0.048	0.670	-0.052	0.048	0.279	-0.034	0.057	0.549	-0.013	0.027	0.639	1.000	0.635	-0.021	0.029	0.480	1.000	0.545
14	rs12566985	-0.013	0.075	0.859	0.028	0.059	0.635	0.057	0.057	0.319	-0.008	0.063	0.898	0.021	0.031	0.511	1.000	0.841	0.028	0.034	0.421	1.000	0.745
15	rs12940622	0.101	0.064	0.114	-0.017	0.045	0.710	0.058	0.044	0.190	0.008	0.049	0.876	0.030	0.024	0.227	1.000	0.402	0.017	0.027	0.516	1.000	0.482
16	rs13021737	-0.136	0.120	0.260	-0.026	0.090	0.772	-0.017	0.074	0.819	-0.047	0.085	0.581	-0.043	0.044	0.328	1.000	0.860	-0.029	0.047	0.544	1.000	0.965
17	rs13201877	0.214	0.178	0.230	-0.192	0.115	0.095	-0.298	0.123	0.015	-0.070	0.116	0.547	-0.132	0.063	0.038	1.000	0.104	-0.182	0.068	0.007	0.518	0.399
18	rs1441264	0.007	0.061	0.911	-0.001	0.046	0.988	0.036	0.041	0.380	0.059	0.045	0.193	0.028	0.023	0.226	1.000	0.797	0.032	0.025	0.206	1.000	0.647
19	rs1460676	0.119	0.060	0.049	0.098	0.046	0.034	-0.079	0.043	0.065	0.006	0.045	0.902	0.022	0.024	0.360	1.000	**0.012**	0.004	0.026	0.880	1.000	**0.019**
20	rs1516725	-0.003	0.109	0.977	-0.016	0.085	0.849	-0.137	0.071	0.053	-0.043	0.087	0.624	-0.064	0.042	0.131	1.000	0.624	-0.075	0.046	0.103	1.000	0.500
21	rs1528435	-0.051	0.061	0.399	0.090	0.046	0.050	0.031	0.047	0.512	0.061	0.048	0.206	0.042	0.025	0.087	1.000	0.299	0.061	0.027	0.024	1.000	0.668
22	rs1558902	0.033	0.085	0.698	-0.053	0.068	0.436	-0.137	0.068	0.045	-0.102	0.080	0.198	-0.072	0.037	0.052	1.000	0.446	-0.096	0.041	0.019	1.000	0.680
23	rs16851483	-0.022	0.064	0.730	0.014	0.050	0.782	0.006	0.048	0.904	0.045	0.054	0.411	0.013	0.027	0.636	1.000	0.882	0.020	0.029	0.498	1.000	0.857

Table 51 (continued): Interaction between 64 SNPs and fiber intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	-0.043	0.059	0.470	0.038	0.041	0.350	0.038	0.041	0.355	-0.079	0.049	0.108	2.93E-04	0.023	0.990	1.000	0.184	0.008	0.025	0.750	1.000	0.121
25	rs17203016	-0.039	0.082	0.634	0.006	0.061	0.918	-0.003	0.056	0.957	-0.026	0.064	0.684	-0.012	0.032	0.716	1.000	0.965	-0.007	0.035	0.846	1.000	0.932
26	rs17405819	0.028	0.061	0.649	-0.013	0.044	0.769	-0.030	0.044	0.486	-0.069	0.047	0.143	-0.026	0.024	0.270	1.000	0.635	-0.036	0.026	0.163	1.000	0.679
27	rs17724992	-0.079	0.058	0.171	0.054	0.044	0.227	-0.020	0.041	0.625	-0.056	0.046	0.229	-0.018	0.023	0.427	1.000	0.222	-0.007	0.025	0.790	1.000	0.215
28	rs1928295	0.085	0.059	0.146	0.044	0.044	0.320	-0.018	0.042	0.675	0.016	0.047	0.741	0.024	0.023	0.298	1.000	0.511	0.013	0.026	0.617	1.000	0.599
29	rs2033529	-0.102	0.086	0.233	0.062	0.060	0.304	0.029	0.052	0.586	0.092	0.059	0.115	0.038	0.031	0.215	1.000	0.293	0.058	0.033	0.075	1.000	0.718
30	rs2033732	-0.037	0.060	0.534	-0.083	0.047	0.078	-0.017	0.042	0.682	0.022	0.046	0.627	-0.027	0.024	0.264	1.000	0.448	-0.025	0.026	0.344	1.000	0.270
31	rs205262	0.053	0.080	0.503	-0.019	0.064	0.771	0.014	0.063	0.828	-0.086	0.068	0.212	-0.013	0.034	0.710	1.000	0.571	-0.027	0.038	0.467	1.000	0.558
32	rs2075650	-0.153	0.116	0.186	0.021	0.084	0.806	-0.003	0.079	0.969	-0.273	0.092	0.003	-0.084	0.045	0.062	1.000	**0.066**	-0.072	0.049	0.142	1.000	**0.034**
33	rs2080454	0.044	0.060	0.469	-0.010	0.043	0.814	-0.006	0.041	0.877	-0.010	0.045	0.824	-0.001	0.023	0.962	1.000	0.884	-0.009	0.025	0.725	1.000	0.997
34	rs2112347	-0.040	0.060	0.505	0.094	0.045	0.035	0.040	0.041	0.335	0.001	0.048	0.982	0.033	0.024	0.158	1.000	0.277	0.047	0.026	0.068	1.000	0.354
35	rs2176040	-0.089	0.118	0.452	0.036	0.089	0.685	-0.066	0.080	0.408	-0.194	0.090	0.031	-0.076	0.046	0.097	1.000	0.340	-0.074	0.050	0.138	1.000	0.188
36	rs2207139	-0.017	0.082	0.840	-0.060	0.062	0.335	-0.038	0.067	0.568	-0.005	0.066	0.937	-0.032	0.034	0.344	1.000	0.938	-0.036	0.037	0.343	1.000	0.833
37	rs2287019	0.116	0.075	0.123	-0.014	0.054	0.789	-0.071	0.054	0.187	-0.040	0.061	0.518	-0.017	0.03	0.561	1.000	0.232	-0.042	0.032	0.195	1.000	0.757
38	rs2365389	0.020	0.088	0.818	-0.050	0.059	0.400	-0.143	0.065	0.028	-0.009	0.074	0.904	-0.056	0.035	0.104	1.000	0.398	-0.071	0.038	0.062	1.000	0.357
39	rs2820292	0.059	0.068	0.383	-0.017	0.058	0.764	-0.023	0.051	0.648	0.074	0.057	0.19	0.018	0.029	0.529	1.000	0.496	0.009	0.032	0.773	1.000	0.379
40	rs2836754	0.049	0.059	0.401	0.043	0.047	0.351	0.057	0.044	0.189	-0.014	0.047	0.771	0.034	0.024	0.160	1.000	0.701	0.031	0.026	0.246	1.000	0.513
41	rs29941	0.086	0.071	0.231	0.045	0.052	0.386	0.038	0.051	0.463	0.001	0.058	0.980	0.039	0.028	0.172	1.000	0.835	0.030	0.031	0.332	1.000	0.839
42	rs3101336	0.018	0.099	0.855	-0.094	0.089	0.294	-0.002	0.077	0.978	-0.029	0.088	0.742	-0.027	0.044	0.541	1.000	0.832	-0.037	0.048	0.442	1.000	0.733
43	rs3817334	-0.023	0.061	0.705	0.059	0.047	0.215	-0.027	0.045	0.546	-0.060	0.050	0.224	-0.011	0.025	0.655	1.000	0.344	-0.009	0.027	0.748	1.000	0.194
44	rs3849570	-0.130	0.056	0.021	-0.001	0.044	0.983	0.007	0.040	0.857	0.107	0.046	0.021	0.006	0.023	0.776	1.000	**0.014**	0.034	0.025	0.178	1.000	0.167
45	rs3888190	0.054	0.097	0.575	0.081	0.077	0.295	-0.036	0.075	0.636	-0.005	0.087	0.958	0.021	0.041	0.606	1.000	0.712	0.014	0.046	0.760	1.000	0.540
46	rs4256980	0.038	0.060	0.531	0.028	0.043	0.513	0.002	0.041	0.958	0.054	0.048	0.260	0.027	0.023	0.238	1.000	0.872	0.026	0.025	0.310	1.000	0.716

Table 51 (continued): Interaction between 64 SNPs and fiber intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	-0.022	0.069	0.756	-0.045	0.052	0.391	0.039	0.049	0.431	-0.003	0.057	0.951	-0.005	0.028	0.867	1.000	0.699	-0.001	0.030	0.962	1.000	0.507
48	rs4787491	-0.075	0.061	0.220	-0.031	0.043	0.475	0.005	0.042	0.910	-0.002	0.047	0.968	-0.019	0.023	0.411	1.000	0.715	-0.010	0.025	0.706	1.000	0.826
49	rs492400	-0.082	0.081	0.307	-0.029	0.053	0.587	0.046	0.049	0.344	0.127	0.053	0.016	0.033	0.028	0.238	1.000	**0.083**	0.048	0.030	0.102	1.000	0.114
50	rs6567160	-0.056	0.084	0.504	0.058	0.058	0.315	0.045	0.058	0.433	0.181	0.064	0.005	0.068	0.032	0.032	1.000	0.137	0.089	0.034	0.009	0.666	0.229
51	rs6804842	-0.029	0.061	0.634	-0.036	0.048	0.456	-0.024	0.044	0.592	0.038	0.047	0.420	-0.011	0.025	0.651	1.000	0.679	-0.008	0.027	0.775	1.000	0.494
52	rs7138803	0.012	0.072	0.868	0.011	0.050	0.820	0.031	0.046	0.501	-0.079	0.052	0.130	-0.005	0.026	0.845	1.000	0.425	-0.008	0.028	0.782	1.000	0.256
53	rs7141420	-0.027	0.060	0.658	-0.042	0.044	0.344	-0.030	0.041	0.464	-0.070	0.046	0.127	-0.043	0.023	0.064	1.000	0.914	-0.046	0.025	0.068	1.000	0.804
54	rs7164727	-0.034	0.071	0.625	-0.045	0.050	0.359	-0.030	0.049	0.540	0.082	0.051	0.110	-0.005	0.027	0.855	1.000	0.264	7.28E-05	0.029	0.998	1.000	0.151
55	rs7239883	-0.024	0.060	0.683	-0.015	0.047	0.751	0.015	0.044	0.738	0.074	0.050	0.139	0.014	0.025	0.561	1.000	0.525	0.022	0.027	0.411	1.000	0.422
56	rs7243357	0.022	0.068	0.742	-0.039	0.053	0.463	0.014	0.058	0.811	-0.082	0.056	0.142	-0.026	0.029	0.365	1.000	0.563	-0.037	0.032	0.247	1.000	0.493
57	rs7599312	0.442	0.185	0.018	-0.064	0.163	0.693	0.124	0.123	0.312	-0.107	0.178	0.548	0.093	0.078	0.234	1.000	0.122	0.018	0.086	0.834	1.000	0.473
58	rs7715256	-0.060	0.170	0.723	-0.067	0.128	0.602	-0.001	0.128	0.992	0.039	0.135	0.776	-0.020	0.069	0.776	1.000	0.941	-0.012	0.075	0.878	1.000	0.848
59	rs7903146	-0.056	0.187	0.765	0.060	0.113	0.593	-0.002	0.157	0.989	0.156	0.155	0.313	0.051	0.073	0.487	1.000	0.823	0.070	0.079	0.378	1.000	0.768
60	rs9374842	0.026	0.129	0.838	-0.071	0.074	0.338	-0.127	0.075	0.091	0.034	0.082	0.677	-0.051	0.042	0.227	1.000	0.468	-0.060	0.044	0.178	1.000	0.343
61	rs9400239	-0.108	0.068	0.114	-0.018	0.049	0.708	0.040	0.044	0.362	0.040	0.051	0.440	0.003	0.026	0.904	1.000	0.254	0.021	0.028	0.438	1.000	0.616
62	rs9641123	-0.122	0.063	0.052	-0.013	0.048	0.791	-0.023	0.043	0.597	-0.026	0.050	0.605	-0.036	0.025	0.142	1.000	0.520	-0.021	0.027	0.448	1.000	0.980
63	rs977747	-0.110	0.145	0.448	0.140	0.111	0.209	-0.073	0.117	0.535	-0.014	0.104	0.896	-0.002	0.058	0.977	1.000	0.464	0.019	0.064	0.763	1.000	0.388
64	rs9914578	0.041	0.070	0.555	0.056	0.055	0.313	0.041	0.052	0.436	0.038	0.059	0.525	0.044	0.029	0.128	1.000	0.996	0.045	0.032	0.161	1.000	0.970

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions (P_{adjust} < 0 .05) and heterogeneity (Q_{pvalue} < 0.1) findings are in bold.

6.3.7.5 %Protein

Table 52 shows the interaction results between 64 SNPs and %protein intake on Z-BMI. None of the interaction remained statistically significant after adjusting for multiple testing. Nominal significant negative SNP × %protein interaction on BMI was observed for *RABEP1* rs1000940 (β=-0.055, SE=0.024, $P_{interaction}$=0.020) and *NEGR1* rs3101336 (β=-0.095, SE=0.041, $P_{interaction}$= 0.020). The BMI level decreased as the number of reported BMI risk alleles and the intake of %protein increased for both SNPs.

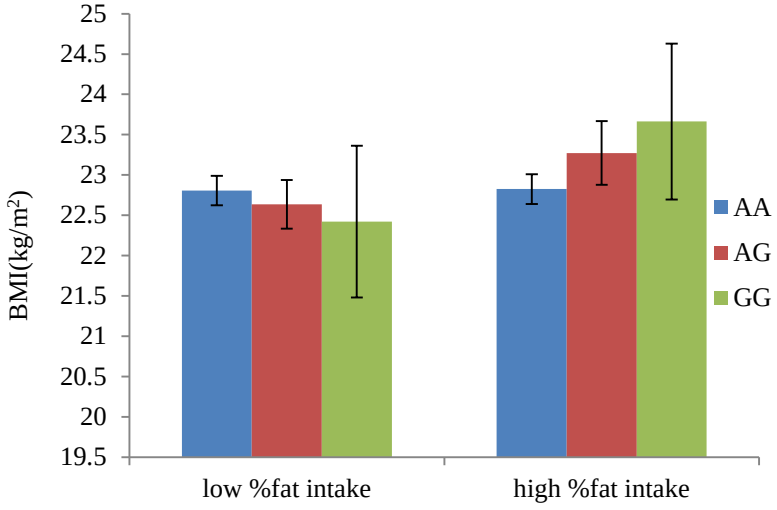
6.3.7.6 %Fat

Table 53 shows the interaction results between 64 SNPs and %fat intake on Z-BMI. Nominal significant SNP × %fat interaction on BMI was observed for *KCNK3* rs11126666 (β=-0.057, SE=0.025, $P_{interaction}$=0.023), *RPTOR* rs12940622 (β=-0.052, SE=0.025, $P_{interaction}$=0.038), *TDRG1* rs2033529 (β=-0.070, SE=0.031, $P_{interaction}$=0.024), *INO80E* rs4787491 (β=-0.055, SE=0.023, $P_{interaction}$=0.018) and *NRXN3* rs7141420 (β=-0.047, SE=0.023, $P_{interaction}$=0.039). For all these SNPs, the interaction terms were negatively associated with Z-BMI so that the BMI level decreased as the number of reported BMI risk alleles and %fat intake increased.

The interaction effect of *C6ofr106* rs205262 with %fat was found to be significant on Z-BMI even after adjusting for multiple comparisons (β=0.122, SE=0.033, $P_{interaction}=1.97\times10^{-4}$, adjusted $P_{interaction}$ =0.015). The positive association between

intake of %fat and BMI tended to be stronger among individuals who are homozygous for the reported BMI risk allele G of rs205262 as compared to individuals who have less copies of the G allele. Figure 14 showed the association between rs205262 and BMI depending on %fat intake using population mean as the cut-off (Mean ± SD: 26.87 ± 5.93). As can be seen, the minor risk allele G would decrease the BMI level in the individuals whose %fat intake was lower than the population mean while increased BMI level in the individuals whose %fat intake was higher than the population mean.

Figure 14: Association of *C6orf106* rs205262 on BMI stratified by %Fat intake



6.3.7.7 %SFA

Table 54 shows the interaction results between 64 SNPs and %SFA intake on Z-BMI. Nominal significant SNP × %SFA interaction on BMI was observed for *TDRG1* rs2033529 (β=-0.078, SE=0.031, $P_{interaction}$=0.011), *C6orf106* rs205262 (β=0.080, SE=0.033, $P_{interaction}$=0.016), *CCDC171* rs4740619 (β=0.058, SE=0.027, $P_{interaction}$=0.034), *INO80E* rs4787491 (β=-0.049, SE=0.023, $P_{interaction}$=0.035) and

Table 52: Interaction between 64 SNPs and %protein intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	-0.155	0.060	0.009	-0.109	0.046	0.019	0.005	0.041	0.901	-0.016	0.046	0.736	-0.055	0.024	0.020	1.000	**0.072**	-0.036	0.026	0.158	1.000	0.162
2	rs1016287	0.102	0.065	0.114	-0.027	0.050	0.586	-0.078	0.049	0.115	0.067	0.052	0.199	0.004	0.027	0.872	1.000	**0.075**	-0.016	0.029	0.593	1.000	0.126
3	rs10182181	0.080	0.056	0.154	0.032	0.043	0.463	-0.077	0.043	0.073	-0.009	0.046	0.849	-0.002	0.023	0.945	1.000	0.121	-0.018	0.025	0.468	1.000	0.196
4	rs10733682	-0.057	0.066	0.388	-0.026	0.053	0.631	-0.013	0.047	0.787	0.021	0.054	0.698	-0.015	0.027	0.576	1.000	0.828	-0.007	0.030	0.821	1.000	0.818
5	rs10938397	0.112	0.069	0.107	-0.021	0.051	0.677	-0.098	0.048	0.044	0.048	0.052	0.358	-0.006	0.027	0.812	1.000	**0.054**	-0.027	0.029	0.346	1.000	0.121
6	rs10968576	-0.055	0.075	0.469	-0.006	0.058	0.912	-0.041	0.057	0.468	-0.118	0.058	0.043	-0.055	0.030	0.073	1.000	0.587	-0.055	0.033	0.100	1.000	0.381
7	rs11030104	0.032	0.059	0.590	-0.006	0.042	0.887	0.087	0.041	0.036	0.005	0.047	0.907	0.031	0.023	0.173	1.000	0.412	0.031	0.025	0.211	1.000	0.238
8	rs11126666	-0.118	0.061	0.052	0.003	0.049	0.958	-0.029	0.047	0.544	-0.071	0.048	0.144	-0.047	0.025	0.061	1.000	0.425	-0.033	0.028	0.242	1.000	0.566
9	rs11191560	-0.015	0.063	0.811	-0.021	0.048	0.669	0.048	0.045	0.280	-0.070	0.052	0.183	-0.009	0.025	0.720	1.000	0.384	-0.008	0.028	0.775	1.000	0.219
10	rs11583200	0.078	0.084	0.353	-0.028	0.073	0.706	0.096	0.076	0.208	0.028	0.096	0.770	0.042	0.041	0.301	1.000	0.656	0.031	0.046	0.505	1.000	0.503
11	rs11688816	-0.003	0.063	0.958	-0.122	0.045	0.007	0.029	0.045	0.517	0.007	0.050	0.891	-0.026	0.025	0.285	1.000	**0.089**	-0.031	0.027	0.254	1.000	**0.041**
12	rs12286929	0.063	0.067	0.347	0.017	0.050	0.726	0.053	0.047	0.262	-0.031	0.052	0.558	0.023	0.026	0.377	1.000	0.608	0.016	0.029	0.576	1.000	0.494
13	rs12429545	-0.017	0.069	0.811	0.055	0.048	0.251	-0.008	0.048	0.863	0.023	0.054	0.673	0.017	0.027	0.512	1.000	0.764	0.023	0.029	0.419	1.000	0.646
14	rs12566985	0.008	0.078	0.917	0.089	0.056	0.111	-0.021	0.052	0.686	-0.022	0.061	0.720	0.014	0.030	0.631	1.000	0.456	0.015	0.032	0.633	1.000	0.272
15	rs12940622	-0.066	0.060	0.273	-0.006	0.048	0.898	-0.003	0.046	0.944	0.035	0.049	0.480	-0.005	0.025	0.838	1.000	0.641	0.008	0.027	0.782	1.000	0.801
16	rs13021737	-0.104	0.119	0.384	-0.138	0.086	0.107	-0.027	0.075	0.719	-0.032	0.090	0.726	-0.069	0.044	0.122	1.000	0.749	-0.063	0.048	0.188	1.000	0.573
17	rs13201877	0.053	0.211	0.802	-0.131	0.093	0.158	0.144	0.105	0.172	-0.105	0.127	0.409	-0.026	0.059	0.653	1.000	0.221	-0.033	0.061	0.589	1.000	0.119
18	rs1441264	-0.013	0.059	0.829	-0.067	0.047	0.153	0.067	0.041	0.102	-0.013	0.046	0.778	-1.40E-04	0.024	0.995	1.000	0.184	0.002	0.026	0.931	1.000	**0.091**
19	rs1460676	-0.017	0.061	0.781	-0.012	0.042	0.783	0.050	0.042	0.235	-0.019	0.046	0.686	0.004	0.023	0.847	1.000	0.639	0.008	0.025	0.747	1.000	0.461
20	rs1516725	-0.066	0.116	0.572	-0.051	0.087	0.554	0.121	0.070	0.085	-0.040	0.094	0.670	0.016	0.044	0.713	1.000	0.297	0.030	0.047	0.531	1.000	0.211
21	rs1528435	0.018	0.066	0.788	-0.101	0.045	0.025	0.004	0.044	0.921	0.006	0.049	0.901	-0.025	0.025	0.316	1.000	0.251	-0.032	0.027	0.235	1.000	0.164
22	rs1558902	0.005	0.082	0.948	0.078	0.062	0.207	0.082	0.067	0.222	-0.141	0.070	0.044	0.013	0.035	0.714	1.000	**0.071**	0.014	0.038	0.708	1.000	**0.030**
23	rs16851483	-0.034	0.067	0.607	-0.035	0.052	0.504	0.052	0.045	0.248	-0.069	0.053	0.196	-0.013	0.026	0.610	1.000	0.326	-0.010	0.029	0.738	1.000	0.188

Table 52 (continued): Interaction between 64 SNPs and %protein intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	0.003	0.059	0.964	-0.033	0.043	0.444	0.024	0.044	0.591	-2.00E-04	0.047	0.997	-0.003	0.024	0.910	1.000	0.834	-0.004	0.026	0.886	1.000	0.652
25	rs17203016	0.044	0.089	0.625	-0.031	0.065	0.628	0.005	0.057	0.935	0.057	0.066	0.390	0.014	0.033	0.679	1.000	0.790	0.009	0.036	0.804	1.000	0.632
26	rs17405819	-0.046	0.063	0.461	-0.041	0.044	0.351	0.007	0.042	0.872	0.030	0.047	0.529	-0.009	0.024	0.712	1.000	0.637	-0.003	0.025	0.921	1.000	0.526
27	rs17724992	-0.109	0.056	0.052	-0.007	0.044	0.872	0.041	0.042	0.333	0.011	0.047	0.814	-0.006	0.023	0.810	1.000	0.192	0.016	0.026	0.534	1.000	0.728
28	rs1928295	-0.021	0.058	0.717	0.001	0.043	0.986	0.071	0.041	0.085	-0.035	0.047	0.464	0.011	0.023	0.635	1.000	0.331	0.017	0.025	0.498	1.000	0.217
29	rs2033529	-0.069	0.081	0.399	-0.091	0.062	0.140	0.054	0.053	0.310	0.006	0.063	0.921	-0.013	0.031	0.675	1.000	0.289	-0.003	0.034	0.918	1.000	0.201
30	rs2033732	-0.034	0.058	0.552	-0.005	0.045	0.919	-0.001	0.042	0.982	-0.114	0.045	0.011	-0.038	0.023	0.103	1.000	0.240	-0.039	0.025	0.129	1.000	0.122
31	rs205262	0.018	0.079	0.822	0.203	0.063	0.001	-0.002	0.063	0.971	-0.046	0.070	0.514	0.051	0.034	0.136	1.000	**0.036**	0.058	0.038	0.122	1.000	**0.015**
32	rs2075650	0.098	0.110	0.376	-0.001	0.082	0.986	-0.048	0.075	0.518	-0.035	0.084	0.675	-0.011	0.043	0.804	1.000	0.725	-0.030	0.046	0.523	1.000	0.912
33	rs2080454	0.088	0.060	0.142	-0.016	0.044	0.714	-0.020	0.042	0.634	0.041	0.045	0.367	0.013	0.023	0.562	1.000	0.391	1.73E-04	0.025	0.995	1.000	0.555
34	rs2112347	0.039	0.057	0.491	0.011	0.044	0.798	-0.018	0.044	0.687	-0.055	0.047	0.241	-0.009	0.024	0.699	1.000	0.586	-0.019	0.026	0.461	1.000	0.588
35	rs2176040	-0.117	0.111	0.293	-0.140	0.089	0.117	-0.044	0.087	0.614	0.006	0.087	0.944	-0.068	0.046	0.140	1.000	0.648	-0.058	0.051	0.253	1.000	0.493
36	rs2207139	-0.008	0.077	0.918	-0.046	0.063	0.464	-0.001	0.064	0.982	0.005	0.066	0.939	-0.014	0.034	0.683	1.000	0.943	-0.015	0.037	0.687	1.000	0.827
37	rs2287019	0.021	0.076	0.779	0.118	0.057	0.037	-0.059	0.053	0.266	-0.027	0.062	0.661	0.011	0.030	0.710	1.000	0.126	0.009	0.033	0.777	1.000	**0.058**
38	rs2365389	0.027	0.082	0.744	-0.037	0.063	0.560	-0.045	0.065	0.489	-0.011	0.071	0.879	-0.022	0.035	0.532	1.000	0.906	-0.032	0.038	0.400	1.000	0.935
39	rs2820292	0.060	0.066	0.363	-0.092	0.055	0.094	-0.037	0.053	0.492	0.009	0.057	0.875	-0.022	0.029	0.440	1.000	0.315	-0.041	0.032	0.196	1.000	0.440
40	rs2836754	-0.062	0.059	0.296	-0.024	0.047	0.602	-0.009	0.043	0.835	-0.065	0.048	0.180	-0.036	0.024	0.137	1.000	0.799	-0.031	0.026	0.247	1.000	0.678
41	rs29941	0.077	0.076	0.316	-0.014	0.053	0.790	-0.058	0.052	0.264	-0.048	0.055	0.387	-0.024	0.029	0.409	1.000	0.495	-0.040	0.031	0.195	1.000	0.824
42	rs3101336	-0.079	0.113	0.484	-0.190	0.080	0.017	-0.079	0.069	0.251	-0.027	0.082	0.739	-0.095	0.041	0.020	1.000	0.535	-0.098	0.044	0.026	1.000	0.340
43	rs3817334	0.023	0.060	0.707	-0.032	0.050	0.523	-0.019	0.047	0.681	-0.044	0.051	0.386	-0.021	0.026	0.408	1.000	0.853	-0.031	0.028	0.274	1.000	0.936
44	rs3849570	-0.019	0.058	0.740	-0.003	0.043	0.936	0.006	0.039	0.880	-0.037	0.049	0.459	-0.010	0.023	0.670	1.000	0.917	-0.008	0.025	0.748	1.000	0.789
45	rs3888190	-0.094	0.109	0.388	0.040	0.083	0.628	0.091	0.074	0.221	0.043	0.079	0.585	0.037	0.042	0.372	1.000	0.576	0.060	0.045	0.184	1.000	0.873
46	rs4256980	0.077	0.065	0.239	0.060	0.045	0.181	-0.069	0.041	0.094	-0.073	0.046	0.112	-0.015	0.024	0.518	1.000	**0.044**	-0.029	0.025	0.248	1.000	**0.055**

Table 52 (continued): Interaction between 64 SNPs and %protein intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	0.016	0.064	0.796	0.039	0.052	0.454	0.032	0.048	0.502	0.062	0.055	0.264	0.038	0.027	0.155	1.000	0.958	0.043	0.030	0.148	1.000	0.917
48	rs4787491	-0.122	0.062	0.049	0.002	0.043	0.966	0.063	0.042	0.131	-0.096	0.047	0.040	-0.021	0.023	0.364	1.000	**0.022**	-0.004	0.025	0.862	1.000	**0.039**
49	rs492400	0.061	0.078	0.436	0.026	0.055	0.643	0.005	0.052	0.930	0.024	0.055	0.655	0.024	0.029	0.413	1.000	0.949	0.018	0.031	0.569	1.000	0.952
50	rs6567160	0.102	0.079	0.197	0.068	0.059	0.246	0.080	0.056	0.155	-0.015	0.061	0.809	0.056	0.031	0.074	1.000	0.594	0.047	0.034	0.164	1.000	0.474
51	rs6804842	-0.034	0.062	0.586	0.046	0.047	0.335	0.070	0.046	0.129	-0.048	0.047	0.306	0.014	0.025	0.573	1.000	0.234	0.023	0.027	0.393	1.000	0.169
52	rs7138803	0.035	0.066	0.595	0.009	0.050	0.850	-0.037	0.049	0.453	0.072	0.054	0.183	0.015	0.027	0.572	1.000	0.505	0.011	0.029	0.704	1.000	0.328
53	rs7141420	0.061	0.058	0.299	-0.105	0.043	0.015	-0.002	0.043	0.955	0.028	0.043	0.516	-0.013	0.023	0.574	1.000	**0.068**	-0.026	0.025	0.293	1.000	**0.072**
54	rs7164727	-0.012	0.064	0.851	-0.009	0.052	0.861	-0.025	0.051	0.627	0.080	0.051	0.119	0.011	0.027	0.692	1.000	0.462	0.016	0.030	0.601	1.000	0.298
55	rs7239883	-0.050	0.064	0.434	-0.067	0.045	0.142	0.007	0.042	0.864	-0.088	0.052	0.088	-0.044	0.025	0.071	1.000	0.484	-0.043	0.027	0.103	1.000	0.295
56	rs7243357	-0.139	0.071	0.050	-1.70E-04	0.052	0.997	-0.011	0.056	0.846	0.005	0.057	0.934	-0.025	0.029	0.389	1.000	0.368	-0.002	0.032	0.946	1.000	0.980
57	rs7599312	0.257	0.194	0.186	-0.045	0.171	0.794	-0.091	0.136	0.503	-0.053	0.144	0.711	-0.014	0.078	0.863	1.000	0.498	-0.066	0.086	0.440	1.000	0.972
58	rs7715256	0.208	0.149	0.163	0.070	0.144	0.624	-0.046	0.104	0.656	-0.116	0.127	0.361	0.005	0.063	0.935	1.000	0.359	-0.040	0.070	0.570	1.000	0.621
59	rs7903146	-0.275	0.226	0.225	0.069	0.150	0.645	0.183	0.182	0.314	0.115	0.145	0.430	0.061	0.084	0.466	1.000	0.425	0.115	0.091	0.204	1.000	0.890
60	rs9374842	-0.141	0.118	0.233	-0.017	0.079	0.829	-0.037	0.078	0.630	-0.137	0.083	0.098	-0.072	0.043	0.094	1.000	0.651	-0.061	0.046	0.183	1.000	0.537
61	rs9400239	0.098	0.064	0.126	-0.025	0.048	0.600	0.014	0.045	0.756	-0.009	0.050	0.856	0.010	0.025	0.678	1.000	0.460	-0.006	0.027	0.834	1.000	0.835
62	rs9641123	-0.038	0.060	0.524	0.052	0.047	0.266	-0.004	0.045	0.934	-0.001	0.050	0.976	0.007	0.025	0.789	1.000	0.664	0.016	0.027	0.562	1.000	0.635
63	rs977747	-0.030	0.177	0.866	0.276	0.111	0.014	-0.195	0.122	0.111	-0.124	0.104	0.233	-0.012	0.061	0.844	1.000	**0.018**	-0.010	0.065	0.882	1.000	**0.007**
64	rs9914578	0.064	0.073	0.377	0.028	0.054	0.607	0.026	0.053	0.622	-0.074	0.060	0.216	0.009	0.029	0.759	1.000	0.435	-0.002	0.032	0.957	1.000	0.361

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions (P_{adjust} < 0 .05) and heterogeneity (Q_{pvalue} < 0.1) findings are in bold.

Table 53: Interaction between 64 SNPs and %fat intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	-0.106	0.060	0.079	0.011	0.046	0.810	0.030	0.042	0.465	-0.089	0.045	0.050	-0.027	0.023	0.244	1.000	0.103	-0.013	0.025	0.603	1.000	0.124
2	rs1016287	0.094	0.065	0.147	-0.032	0.051	0.539	-0.024	0.051	0.634	-0.024	0.051	0.641	-0.006	0.027	0.829	1.000	0.410	-0.027	0.030	0.369	1.000	0.993
3	rs10182181	0.056	0.060	0.352	0.064	0.044	0.146	-0.022	0.044	0.615	-0.071	0.046	0.124	0.002	0.024	0.926	1.000	0.133	-0.008	0.026	0.765	1.000	**0.098**
4	rs10733682	-0.010	0.070	0.883	-0.005	0.055	0.925	-0.023	0.047	0.626	0.025	0.055	0.654	-0.005	0.028	0.867	1.000	0.932	-0.004	0.030	0.905	1.000	0.805
5	rs10938397	0.044	0.065	0.497	0.012	0.050	0.814	0.036	0.047	0.452	0.014	0.052	0.788	0.025	0.026	0.342	1.000	0.969	0.021	0.029	0.460	1.000	0.929
6	rs10968576	-0.050	0.073	0.493	0.004	0.057	0.951	-0.064	0.054	0.236	-0.135	0.062	0.031	-0.059	0.030	0.050	1.000	0.437	-0.061	0.033	0.066	1.000	0.259
7	rs11030104	-0.008	0.057	0.896	-0.010	0.042	0.816	0.025	0.040	0.526	-0.084	0.045	0.063	-0.017	0.022	0.457	1.000	0.336	-0.018	0.024	0.452	1.000	0.187
8	rs11126666	-0.141	0.060	0.018	-0.029	0.048	0.549	-0.017	0.045	0.713	-0.074	0.049	0.129	-0.057	0.025	0.023	1.000	0.356	-0.039	0.027	0.157	1.000	0.669
9	rs11191560	0.030	0.063	0.639	0.054	0.049	0.270	0.015	0.047	0.741	-0.067	0.054	0.219	0.010	0.026	0.703	1.000	0.405	0.006	0.029	0.838	1.000	0.247
10	rs11583200	0.122	0.091	0.182	0.010	0.078	0.896	-0.018	0.080	0.826	0.082	0.089	0.357	0.042	0.042	0.314	1.000	0.639	0.021	0.047	0.660	1.000	0.697
11	rs11688816	0.074	0.062	0.238	-0.116	0.047	0.013	-0.068	0.045	0.131	0.028	0.049	0.570	-0.035	0.025	0.163	1.000	**0.042**	-0.055	0.027	0.042	1.000	**0.099**
12	rs12286929	0.003	0.065	0.959	-0.006	0.048	0.907	-0.037	0.050	0.459	-0.014	0.050	0.777	-0.015	0.026	0.564	1.000	0.957	-0.019	0.029	0.514	1.000	0.897
13	rs12429545	-0.049	0.067	0.464	0.099	0.048	0.037	-0.008	0.048	0.877	0.114	0.052	0.030	0.049	0.026	0.061	1.000	0.105	0.067	0.028	0.019	1.000	0.163
14	rs12566985	-0.006	0.073	0.931	0.104	0.056	0.065	-0.034	0.056	0.546	0.024	0.059	0.688	0.025	0.030	0.406	1.000	0.353	0.031	0.033	0.342	1.000	0.219
15	rs12940622	-0.127	0.061	0.038	-0.068	0.049	0.159	-0.019	0.044	0.667	-0.026	0.050	0.602	-0.052	0.025	0.038	1.000	0.488	-0.037	0.027	0.178	1.000	0.730
16	rs13021737	-0.158	0.119	0.186	-0.042	0.089	0.633	-0.019	0.080	0.809	-0.097	0.098	0.324	-0.065	0.047	0.167	1.000	0.776	-0.048	0.051	0.348	1.000	0.826
17	rs13201877	0.333	0.191	0.082	-0.095	0.100	0.341	0.120	0.105	0.254	-0.084	0.110	0.441	0.011	0.058	0.844	1.000	0.122	-0.021	0.060	0.731	1.000	0.261
18	rs1441264	0.009	0.059	0.876	-0.032	0.046	0.485	0.084	0.042	0.046	0.007	0.047	0.878	0.022	0.024	0.360	1.000	0.297	0.024	0.026	0.352	1.000	0.162
19	rs1460676	-0.059	0.060	0.325	0.036	0.045	0.419	0.027	0.043	0.533	0.019	0.046	0.679	0.014	0.024	0.554	1.000	0.607	0.027	0.026	0.286	1.000	0.963
20	rs1516725	-0.117	0.106	0.272	-0.151	0.087	0.082	0.150	0.073	0.039	-0.003	0.090	0.976	-0.004	0.043	0.918	1.000	**0.037**	0.018	0.047	0.706	1.000	**0.028**
21	rs1528435	-0.075	0.062	0.232	-0.089	0.045	0.045	-0.019	0.044	0.655	0.015	0.046	0.744	-0.039	0.024	0.107	1.000	0.365	-0.032	0.026	0.211	1.000	0.249
22	rs1558902	0.028	0.086	0.742	0.045	0.064	0.479	-3.10E-04	0.066	0.996	-0.039	0.073	0.599	0.010	0.035	0.785	1.000	0.847	0.006	0.039	0.881	1.000	0.685
23	rs16851483	-0.045	0.065	0.490	0.034	0.052	0.505	0.008	0.046	0.858	-0.102	0.052	0.048	-0.022	0.026	0.397	1.000	0.245	-0.018	0.029	0.536	1.000	0.134

Table 53 (continued): Interaction between 64 SNPs and %fat intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	0.039	0.060	0.514	-0.014	0.043	0.750	-0.005	0.045	0.917	0.008	0.046	0.858	0.003	0.024	0.908	1.000	0.906	-0.004	0.026	0.878	1.000	0.941
25	rs17203016	-0.095	0.087	0.276	-0.070	0.064	0.271	0.008	0.059	0.890	0.037	0.069	0.593	-0.023	0.034	0.504	1.000	0.519	-0.010	0.037	0.791	1.000	0.484
26	rs17405819	-0.083	0.061	0.172	-0.040	0.044	0.362	-0.074	0.042	0.080	0.071	0.047	0.132	-0.029	0.024	0.213	1.000	**0.089**	-0.020	0.026	0.439	1.000	**0.061**
27	rs17724992	-0.092	0.059	0.117	-0.025	0.044	0.574	-0.040	0.041	0.319	0.037	0.047	0.426	-0.025	0.023	0.276	1.000	0.359	-0.013	0.025	0.608	1.000	0.431
28	rs1928295	-0.013	0.056	0.812	-0.008	0.044	0.855	0.003	0.042	0.943	-0.035	0.046	0.449	-0.012	0.023	0.592	1.000	0.944	-0.012	0.025	0.631	1.000	0.826
29	rs2033529	-0.166	0.081	0.042	-0.037	0.059	0.528	-0.080	0.053	0.133	-0.036	0.063	0.562	-0.070	0.031	0.024	1.000	0.568	-0.054	0.033	0.108	1.000	0.817
30	rs2033732	0.009	0.057	0.873	-0.079	0.046	0.091	-0.020	0.042	0.645	-0.015	0.047	0.745	-0.029	0.024	0.223	1.000	0.633	-0.037	0.026	0.158	1.000	0.552
31	rs205262	-0.026	0.080	0.749	0.139	0.061	0.023	0.169	0.059	0.004	0.143	0.067	0.033	0.122	0.033	**1.97E-04**	**0.015**	0.236	0.151	0.036	**2.39E-05**	**0.002**	0.928
32	rs2075650	0.003	0.103	0.979	-0.023	0.083	0.782	-0.097	0.073	0.185	-0.055	0.091	0.545	-0.051	0.043	0.234	1.000	0.853	-0.062	0.047	0.187	1.000	0.795
33	rs2080454	0.011	0.059	0.852	0.008	0.044	0.856	-0.011	0.042	0.786	0.011	0.046	0.805	0.003	0.023	0.884	1.000	0.980	0.002	0.025	0.938	1.000	0.922
34	rs2112347	-0.048	0.056	0.387	0.025	0.045	0.581	0.017	0.042	0.681	0.029	0.047	0.540	0.011	0.023	0.651	1.000	0.707	0.023	0.026	0.367	1.000	0.982
35	rs2176040	-0.167	0.112	0.138	-0.066	0.088	0.453	0.014	0.079	0.856	-0.185	0.089	0.038	-0.086	0.045	0.055	1.000	0.329	-0.071	0.049	0.149	1.000	0.244
36	rs2207139	-0.028	0.079	0.721	-0.003	0.064	0.960	0.067	0.064	0.298	-0.054	0.068	0.431	-0.001	0.034	0.984	1.000	0.607	0.006	0.038	0.882	1.000	0.430
37	rs2287019	0.135	0.074	0.067	0.081	0.056	0.152	-0.038	0.052	0.468	-0.063	0.062	0.313	0.018	0.030	0.545	1.000	0.086	-0.005	0.033	0.881	1.000	0.167
38	rs2365389	-0.007	0.081	0.930	-0.057	0.061	0.343	0.060	0.065	0.352	-0.011	0.069	0.878	-0.005	0.034	0.879	1.000	0.621	-0.005	0.037	0.898	1.000	0.412
39	rs2820292	0.008	0.068	0.906	0.024	0.057	0.671	-0.006	0.051	0.904	-0.002	0.059	0.969	0.005	0.029	0.858	1.000	0.981	0.005	0.032	0.887	1.000	0.916
40	rs2836754	-0.008	0.061	0.898	0.002	0.045	0.966	-0.090	0.042	0.031	0.051	0.050	0.309	-0.019	0.024	0.436	1.000	0.165	-0.021	0.026	0.428	1.000	**0.080**
41	rs29941	0.137	0.075	0.069	0.081	0.052	0.122	-0.009	0.051	0.856	-0.099	0.055	0.071	0.014	0.028	0.626	1.000	**0.032**	-0.006	0.030	0.834	1.000	**0.059**
42	rs3101336	-0.085	0.106	0.421	-0.175	0.086	0.042	-0.014	0.069	0.843	0.076	0.097	0.432	-0.048	0.043	0.263	1.000	0.240	-0.041	0.047	0.386	1.000	0.132
43	rs3817334	-0.002	0.062	0.974	-0.065	0.050	0.188	-0.051	0.047	0.286	-0.028	0.049	0.565	-0.040	0.026	0.116	1.000	0.863	-0.048	0.028	0.087	1.000	0.868
44	rs3849570	-0.011	0.059	0.852	-0.041	0.044	0.348	0.017	0.041	0.672	-0.089	0.047	0.058	-0.030	0.023	0.204	1.000	0.377	-0.033	0.025	0.193	1.000	0.225
45	rs3888190	-0.058	0.109	0.594	0.048	0.084	0.566	0.120	0.072	0.099	-0.007	0.080	0.926	0.041	0.042	0.324	1.000	0.497	0.058	0.045	0.198	1.000	0.494
46	rs4256980	0.051	0.063	0.423	0.017	0.045	0.711	0.057	0.043	0.181	-0.023	0.047	0.622	0.024	0.024	0.316	1.000	0.613	0.020	0.026	0.450	1.000	0.449

Table 53 (continued): Interaction between 64 SNPs and %fat intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	0.076	0.064	0.237	0.057	0.052	0.267	0.010	0.049	0.834	0.022	0.055	0.696	0.038	0.027	0.163	1.000	0.829	0.030	0.030	0.325	1.000	0.794
48	rs4787491	-0.121	0.060	0.044	-0.028	0.043	0.514	0.005	0.042	0.904	-0.119	0.046	0.010	-0.055	0.023	0.018	1.000	0.133	-0.043	0.025	0.084	1.000	0.124
49	rs492400	0.033	0.073	0.648	-0.013	0.054	0.807	0.007	0.052	0.899	0.062	0.055	0.263	0.020	0.028	0.488	1.000	0.787	0.017	0.031	0.576	1.000	0.601
50	rs6567160	0.041	0.076	0.585	0.042	0.060	0.476	-0.085	0.053	0.106	0.039	0.064	0.536	-0.002	0.031	0.956	1.000	0.284	-0.010	0.034	0.763	1.000	0.181
51	rs6804842	0.002	0.064	0.970	0.043	0.046	0.342	-0.014	0.044	0.751	-0.003	0.048	0.958	0.008	0.024	0.751	1.000	0.824	0.009	0.026	0.743	1.000	0.638
52	rs7138803	-0.045	0.064	0.478	0.052	0.050	0.295	-0.061	0.045	0.177	-0.002	0.054	0.964	-0.014	0.026	0.591	1.000	0.370	-0.008	0.028	0.785	1.000	0.240
53	rs7141420	-0.011	0.060	0.856	-0.016	0.043	0.706	-0.076	0.041	0.067	-0.067	0.045	0.134	-0.047	0.023	0.039	1.000	0.670	-0.054	0.025	0.031	1.000	0.573
54	rs7164727	-0.108	0.070	0.122	-0.025	0.049	0.606	0.035	0.050	0.487	0.021	0.052	0.688	-0.008	0.027	0.767	1.000	0.359	0.009	0.029	0.748	1.000	0.667
55	rs7239883	0.019	0.061	0.756	-0.032	0.048	0.506	-0.013	0.045	0.777	-0.034	0.051	0.508	-0.018	0.025	0.480	1.000	0.906	-0.025	0.027	0.361	1.000	0.939
56	rs7243357	-0.157	0.066	0.018	-0.026	0.054	0.628	0.045	0.058	0.441	-0.028	0.056	0.622	-0.034	0.029	0.238	1.000	0.148	-0.005	0.032	0.883	1.000	0.591
57	rs7599312	0.098	0.195	0.616	-0.103	0.173	0.551	0.001	0.123	0.991	-0.029	0.160	0.856	-0.012	0.078	0.881	1.000	0.892	-0.032	0.085	0.703	1.000	0.885
58	rs7715256	0.065	0.150	0.667	0.153	0.131	0.240	-0.053	0.109	0.628	-0.049	0.112	0.659	0.013	0.061	0.831	1.000	0.583	0.003	0.067	0.967	1.000	0.405
59	rs7903146	-0.301	0.254	0.236	-0.087	0.131	0.506	0.348	0.173	0.045	-0.186	0.177	0.295	-0.030	0.085	0.727	1.000	**0.077**	0.004	0.090	0.960	1.000	**0.062**
60	rs9374842	-0.097	0.119	0.413	-0.026	0.079	0.743	0.031	0.073	0.673	-0.045	0.075	0.552	-0.022	0.041	0.590	1.000	0.796	-0.012	0.044	0.786	1.000	0.754
61	rs9400239	0.028	0.063	0.659	0.003	0.045	0.945	0.032	0.046	0.479	-0.095	0.051	0.061	-0.008	0.025	0.746	1.000	0.250	-0.015	0.027	0.588	1.000	0.156
62	rs9641123	-0.016	0.061	0.797	0.035	0.046	0.457	-0.001	0.044	0.979	0.044	0.049	0.367	0.018	0.025	0.468	1.000	0.823	0.024	0.027	0.365	1.000	0.760
63	rs977747	-0.056	0.176	0.753	0.200	0.115	0.083	0.086	0.117	0.461	-0.097	0.103	0.349	0.038	0.060	0.525	1.000	0.247	0.051	0.064	0.429	1.000	0.148
64	rs9914578	0.063	0.075	0.399	0.035	0.053	0.505	0.016	0.052	0.753	-0.089	0.059	0.131	0.004	0.029	0.902	1.000	0.317	-0.007	0.031	0.824	1.000	0.249

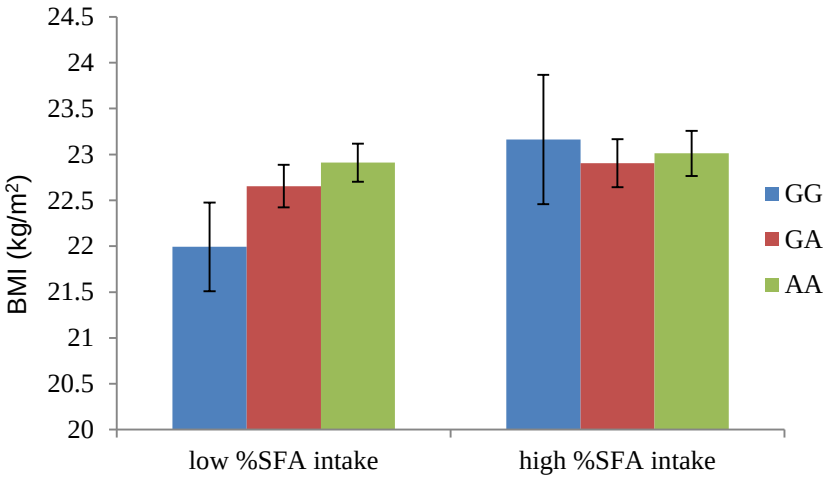
Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions (P_{adjust} < 0 .05) and heterogeneity (Q_{pvalue} < 0.1) findings are in bold.

NRXN3 rs7141420 (β=-0.049, SE=0.023, $P_{interaction}$=0.033). In the case of rs205262 and rs4740619, the interaction term was found to be positively associated with Z-BMI. Thus BMI level increased as the number of reported BMI risk alleles and the intake of %SFA increased. For the rest SNPs, the interaction terms were negatively associated with Z-BMI so that the BMI level decreased as the number of reported BMI risk alleles and the intake of %SFA increased.

The interaction effect of *KCNK3* rs11126666 with %SFA was found to be significant on Z-BMI even after adjusting for multiple comparisons (β=-0.086 SE=0.025, $P_{interaction}=5.91\times10^{-4}$, adjusted $P_{interaction}$ =0.044). The negative association between %SFA intake and BMI tended to be stronger among individuals who are homozygous for the reported BMI non-risk allele G of rs11126666 as compared to individuals who have less copies of the G allele. Figure 15 showed the association between rs11126666 and BMI depending on %SFA intake using population mean as the cut-off (Mean ± SD: 9.81 ± 2.76). As can be seen, the major risk allele A would increase the BMI level in the individuals whose %SFA intake was lower than the population mean while decreased BMI level in the individuals whose %SFA intake was higher than the population mean.

Since an interaction was found between rs11126666 and %SFA on Z-BMI, we further investigated whether the interaction was driven by a subtype of SFA (Table 55). None of the interaction remained significant after Bonferroni correction (P<0.008=0.05/6).

Figure 15: Association of *KCNK3* rs11126666 on BMI stratified by %SFA intake



6.3.7.8 %MFA

Table 56 shows the interaction results between 64 SNPs and %MFA intake on Z-BMI. None of the interaction remained statistically significant after correction for multiple comparisons. Nominal significant SNP × %MFA interaction on BMI was observed for *C6orf106* rs205262 (β=0.108, SE=0.033, $P_{interaction}$= 0.001) and *KCNK3* rs11126666 (β=-0.056, SE=0.025, $P_{interaction}$=0.027). In the case of rs11126666, BMI level decreased as the number of A allele and the intake of %MFA increased while for rs205262, BMI level increased as the number of G allele and %MFA intake increased.

In addition, if meta-analysis was conducted only in SCHS controls and SP2, the interaction between rs205262 and %MFA on Z-BMI would still be significant after correction for multiple testing (β=0.136, SE=0.036, $P_{interaction}=1.47\times10^{-4}$, P_{adjust}=0.011).

Table 54: Interaction between 64 SNPs and %SFA intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	-0.115	0.062	0.062	0.037	0.046	0.416	0.037	0.041	0.368	-0.075	0.046	0.105	-0.014	0.024	0.549	1.000	**0.065**	0.003	0.025	0.902	1.000	0.129
2	rs1016287	0.108	0.065	0.096	-0.014	0.052	0.784	-0.078	0.051	0.130	-0.038	0.052	0.464	-0.017	0.027	0.530	1.000	0.152	-0.044	0.030	0.144	1.000	0.677
3	rs10182181	0.040	0.060	0.501	0.065	0.045	0.146	0.003	0.044	0.943	-0.074	0.046	0.106	0.005	0.024	0.819	1.000	0.161	-0.001	0.026	0.968	1.000	**0.093**
4	rs10733682	0.048	0.070	0.490	-0.023	0.055	0.674	0.003	0.048	0.949	-0.040	0.057	0.483	-0.007	0.028	0.806	1.000	0.779	-0.017	0.031	0.569	1.000	0.840
5	rs10938397	0.118	0.065	0.069	0.032	0.050	0.523	-0.032	0.048	0.503	-0.081	0.054	0.135	-4.33E-04	0.027	0.987	1.000	**0.093**	-0.025	0.029	0.401	1.000	0.303
6	rs10968576	-0.070	0.070	0.320	-0.050	0.058	0.387	0.007	0.055	0.901	-0.085	0.061	0.163	-0.045	0.030	0.133	1.000	0.693	-0.040	0.033	0.234	1.000	0.522
7	rs11030104	0.031	0.057	0.583	0.048	0.043	0.265	0.064	0.041	0.117	-0.037	0.044	0.399	0.028	0.023	0.217	1.000	0.363	0.027	0.025	0.268	1.000	0.203
8	rs11126666	-0.136	0.060	0.023	-0.045	0.049	0.357	-0.097	0.045	0.032	-0.082	0.050	0.103	-0.086	0.025	**5.91E-04**	**0.044**	0.685	-0.076	0.028	0.006	0.444	0.726
9	rs11191560	-0.003	0.062	0.963	0.062	0.048	0.194	0.031	0.048	0.522	-0.035	0.055	0.528	0.019	0.026	0.459	1.000	0.583	0.024	0.029	0.401	1.000	0.408
10	rs11583200	0.098	0.093	0.295	0.029	0.078	0.711	0.007	0.080	0.931	0.048	0.088	0.587	0.041	0.042	0.327	1.000	0.901	0.027	0.047	0.571	1.000	0.943
11	rs11688816	0.074	0.060	0.221	-0.027	0.049	0.584	-0.101	0.046	0.027	0.043	0.049	0.380	-0.014	0.025	0.587	1.000	**0.067**	-0.032	0.028	0.246	1.000	**0.099**
12	rs12286929	-0.016	0.066	0.810	-0.075	0.047	0.107	-0.058	0.050	0.243	-0.026	0.051	0.617	-0.048	0.026	0.063	1.000	0.848	-0.055	0.028	0.055	1.000	0.772
13	rs12429545	-0.118	0.067	0.078	0.095	0.047	0.042	-0.012	0.048	0.794	0.141	0.054	0.009	0.041	0.026	0.113	1.000	**0.008**	0.070	0.028	0.014	1.000	**0.081**
14	rs12566985	0.001	0.074	0.991	0.086	0.054	0.112	-0.080	0.055	0.143	0.038	0.060	0.535	0.012	0.030	0.698	1.000	0.179	0.014	0.033	0.675	1.000	**0.087**
15	rs12940622	-0.139	0.064	0.029	-0.091	0.048	0.058	0.001	0.045	0.985	-0.007	0.049	0.888	-0.048	0.025	0.057	1.000	0.190	-0.031	0.027	0.255	1.000	0.313
16	rs13021737	-0.021	0.108	0.846	0.022	0.082	0.792	-0.031	0.077	0.687	-0.090	0.100	0.367	-0.025	0.045	0.567	1.000	0.860	-0.026	0.049	0.589	1.000	0.686
17	rs13201877	0.368	0.178	0.040	-0.008	0.107	0.939	0.149	0.105	0.157	-0.121	0.120	0.314	0.057	0.060	0.340	1.000	**0.095**	0.018	0.064	0.781	1.000	0.229
18	rs1441264	-0.008	0.060	0.894	-0.024	0.046	0.606	0.107	0.042	0.011	0.045	0.047	0.341	0.038	0.024	0.110	1.000	0.164	0.046	0.026	0.072	1.000	0.110
19	rs1460676	-0.098	0.060	0.102	-0.005	0.046	0.913	0.033	0.044	0.457	0.034	0.044	0.444	0.002	0.024	0.919	1.000	0.281	0.021	0.026	0.411	1.000	0.789
20	rs1516725	-0.180	0.102	0.078	-0.163	0.088	0.064	0.161	0.070	0.021	0.038	0.091	0.671	-0.001	0.042	0.985	1.000	**0.007**	0.037	0.047	0.430	1.000	**0.015**
21	rs1528435	-0.056	0.061	0.358	-0.074	0.045	0.099	-0.004	0.043	0.932	-0.048	0.048	0.315	-0.043	0.024	0.072	1.000	0.716	-0.041	0.026	0.118	1.000	0.521
22	rs1558902	-0.052	0.082	0.523	0.068	0.063	0.284	0.048	0.067	0.472	-0.026	0.076	0.738	0.020	0.035	0.581	1.000	0.597	0.036	0.039	0.358	1.000	0.626
23	rs16851483	-0.013	0.066	0.839	0.023	0.052	0.655	-0.017	0.047	0.714	-0.050	0.053	0.348	-0.014	0.027	0.595	1.000	0.807	-0.014	0.029	0.624	1.000	0.614

Table 54 (continued): Interaction between 64 SNPs and %SFA intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	0.061	0.059	0.304	-0.014	0.043	0.749	-0.002	0.043	0.957	0.041	0.047	0.376	0.015	0.023	0.522	1.000	0.674	0.007	0.025	0.797	1.000	0.662
25	rs17203016	-0.139	0.089	0.117	-0.077	0.066	0.242	-0.013	0.058	0.825	0.012	0.065	0.857	-0.041	0.033	0.221	1.000	0.489	-0.025	0.036	0.495	1.000	0.610
26	rs17405819	-0.118	0.060	0.049	-0.039	0.044	0.371	-0.019	0.043	0.654	0.050	0.048	0.291	-0.023	0.024	0.324	1.000	0.168	-0.006	0.026	0.824	1.000	0.355
27	rs17724992	-0.073	0.060	0.223	-0.051	0.044	0.242	-0.047	0.041	0.250	0.054	0.047	0.248	-0.027	0.023	0.241	1.000	0.246	-0.019	0.025	0.449	1.000	0.178
28	rs1928295	0.012	0.059	0.837	-0.027	0.045	0.542	-0.003	0.041	0.943	-0.017	0.046	0.712	-0.011	0.023	0.643	1.000	0.952	-0.015	0.025	0.554	1.000	0.921
29	rs2033529	-0.190	0.082	0.021	-0.071	0.057	0.215	-0.024	0.053	0.657	-0.097	0.063	0.122	-0.078	0.031	0.011	0.814	0.391	-0.060	0.033	0.070	1.000	0.651
30	rs2033732	0.031	0.058	0.599	-0.098	0.046	0.034	0.002	0.043	0.961	0.032	0.048	0.502	-0.013	0.024	0.601	1.000	0.175	-0.021	0.026	0.418	1.000	0.117
31	rs205262	-0.035	0.081	0.666	0.068	0.060	0.257	0.110	0.063	0.080	0.139	0.067	0.038	0.080	0.033	0.016	1.000	0.383	0.103	0.036	0.005	0.37	0.729
32	rs2075650	0.006	0.106	0.955	-0.066	0.081	0.414	-0.105	0.074	0.154	-0.003	0.096	0.975	-0.055	0.043	0.206	1.000	0.776	-0.067	0.047	0.158	1.000	0.701
33	rs2080454	-0.008	0.058	0.895	0.027	0.044	0.543	-0.043	0.042	0.307	0.038	0.045	0.399	0.003	0.023	0.884	1.000	0.548	0.005	0.025	0.828	1.000	0.354
34	rs2112347	-0.047	0.057	0.404	-0.039	0.046	0.398	0.033	0.041	0.430	0.033	0.047	0.487	4.12E-04	0.023	0.986	1.000	0.471	0.010	0.026	0.690	1.000	0.435
35	rs2176040	-0.161	0.109	0.138	0.056	0.085	0.507	0.023	0.078	0.767	-0.062	0.092	0.503	-0.019	0.045	0.678	1.000	0.391	0.010	0.049	0.833	1.000	0.628
36	rs2207139	-0.001	0.076	0.994	0.040	0.065	0.538	0.007	0.063	0.909	-0.096	0.063	0.128	-0.014	0.033	0.667	1.000	0.471	-0.017	0.037	0.635	1.000	0.289
37	rs2287019	0.089	0.073	0.221	0.059	0.056	0.287	-0.015	0.051	0.768	-0.041	0.061	0.501	0.016	0.029	0.576	1.000	0.413	0.002	0.032	0.943	1.000	0.434
38	rs2365389	0.060	0.083	0.468	-0.009	0.063	0.890	0.108	0.065	0.098	-0.021	0.067	0.751	0.032	0.034	0.354	1.000	0.472	0.026	0.038	0.491	1.000	0.304
39	rs2820292	-0.031	0.069	0.653	0.007	0.056	0.895	-0.004	0.052	0.939	0.035	0.057	0.540	0.004	0.029	0.883	1.000	0.901	0.012	0.032	0.711	1.000	0.877
40	rs2836754	-0.014	0.061	0.825	-0.029	0.045	0.527	-0.098	0.042	0.019	0.026	0.050	0.599	-0.036	0.024	0.130	1.000	0.271	-0.040	0.026	0.121	1.000	0.153
41	rs29941	0.107	0.076	0.162	0.089	0.052	0.089	0.023	0.052	0.661	-0.088	0.055	0.113	0.025	0.028	0.384	1.000	**0.078**	0.012	0.031	0.707	1.000	**0.065**
42	rs3101336	0.019	0.097	0.847	0.015	0.086	0.861	0.028	0.071	0.694	0.151	0.089	0.090	0.051	0.042	0.229	1.000	0.649	0.058	0.047	0.214	1.000	0.469
43	rs3817334	0.002	0.061	0.978	-0.029	0.050	0.553	-0.013	0.049	0.784	-0.011	0.050	0.819	-0.015	0.026	0.575	1.000	0.983	-0.018	0.029	0.527	1.000	0.961
44	rs3849570	-0.026	0.058	0.657	-0.030	0.045	0.510	0.013	0.041	0.762	-0.027	0.047	0.569	-0.015	0.023	0.527	1.000	0.885	-0.013	0.026	0.620	1.000	0.739
45	rs3888190	-0.026	0.112	0.815	0.011	0.086	0.894	0.063	0.071	0.374	0.023	0.083	0.778	0.027	0.042	0.515	1.000	0.915	0.036	0.046	0.425	1.000	0.883
46	rs4256980	0.077	0.063	0.221	-2.60E-04	0.044	0.995	0.055	0.041	0.182	-0.047	0.048	0.320	0.017	0.024	0.468	1.000	0.291	0.007	0.025	0.775	1.000	0.261

Table 54 (continued): Interaction between 64 SNPs and %SFA intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	0.097	0.064	0.131	0.087	0.052	0.098	0.028	0.049	0.561	0.034	0.057	0.548	0.058	0.027	0.034	1.000	0.748	0.049	0.030	0.102	1.000	0.681
48	rs4787491	-0.086	0.060	0.148	-0.028	0.043	0.506	-0.010	0.042	0.810	-0.096	0.046	0.037	-0.049	0.023	0.035	1.000	0.469	-0.042	0.025	0.094	1.000	0.355
49	rs492400	0.009	0.071	0.900	-0.031	0.051	0.547	0.011	0.052	0.828	0.003	0.054	0.961	-0.004	0.028	0.894	1.000	0.938	-0.006	0.030	0.842	1.000	0.830
50	rs6567160	0.028	0.078	0.717	0.003	0.062	0.962	-0.066	0.055	0.233	0.058	0.062	0.352	-0.001	0.031	0.968	1.000	0.490	-0.007	0.034	0.839	1.000	0.325
51	rs6804842	0.008	0.062	0.893	0.051	0.046	0.264	-0.033	0.044	0.464	0.080	0.047	0.091	0.027	0.024	0.263	1.000	0.331	0.031	0.026	0.246	1.000	0.191
52	rs7138803	-0.066	0.063	0.294	0.087	0.051	0.085	-0.024	0.046	0.612	0.020	0.053	0.706	0.009	0.026	0.720	1.000	0.227	0.025	0.029	0.384	1.000	0.271
53	rs7141420	-0.015	0.060	0.799	-0.015	0.044	0.731	-0.084	0.042	0.047	-0.062	0.043	0.149	-0.049	0.023	0.033	1.000	0.643	-0.055	0.025	0.028	1.000	0.522
54	rs7164727	-0.191	0.073	0.009	-0.005	0.051	0.923	0.011	0.050	0.825	-0.057	0.051	0.269	-0.041	0.027	0.133	1.000	0.114	-0.016	0.029	0.578	1.000	0.616
55	rs7239883	0.057	0.063	0.362	-0.029	0.049	0.552	-0.017	0.045	0.713	-0.014	0.051	0.780	-0.007	0.025	0.774	1.000	0.725	-0.020	0.028	0.473	1.000	0.974
56	rs7243357	-0.136	0.065	0.037	-0.021	0.055	0.706	0.038	0.057	0.504	-0.054	0.057	0.339	-0.037	0.029	0.198	1.000	0.236	-0.013	0.032	0.697	1.000	0.508
57	rs7599312	0.024	0.220	0.914	-0.361	0.175	0.040	-0.028	0.122	0.816	-0.081	0.182	0.654	-0.104	0.082	0.203	1.000	0.411	-0.124	0.088	0.157	1.000	0.288
58	rs7715256	0.027	0.149	0.856	0.180	0.133	0.178	-0.119	0.129	0.356	0.007	0.120	0.951	0.020	0.066	0.759	1.000	0.455	0.019	0.073	0.801	1.000	0.271
59	rs7903146	-0.252	0.268	0.348	-0.207	0.140	0.140	0.267	0.154	0.084	-0.161	0.140	0.252	-0.070	0.080	0.381	1.000	**0.086**	-0.052	0.083	0.532	1.000	**0.047**
60	rs9374842	-0.188	0.126	0.136	-0.040	0.078	0.606	0.050	0.069	0.467	-0.097	0.070	0.169	-0.043	0.040	0.276	1.000	0.291	-0.027	0.042	0.513	1.000	0.322
61	rs9400239	0.019	0.062	0.753	0.007	0.046	0.878	0.091	0.046	0.049	-0.053	0.052	0.315	0.020	0.025	0.421	1.000	0.226	0.021	0.028	0.459	1.000	0.113
62	rs9641123	0.017	0.063	0.787	-0.011	0.048	0.814	-0.036	0.043	0.405	0.045	0.050	0.360	-0.001	0.025	0.971	1.000	0.647	-0.004	0.027	0.877	1.000	0.458
63	rs977747	-0.063	0.187	0.734	0.143	0.111	0.197	0.046	0.114	0.686	-0.041	0.104	0.698	0.035	0.060	0.562	1.000	0.624	0.046	0.063	0.467	1.000	0.484
64	rs9914578	0.014	0.073	0.847	-0.016	0.054	0.772	-0.009	0.051	0.867	-0.035	0.060	0.564	-0.013	0.029	0.651	1.000	0.964	-0.018	0.032	0.565	1.000	0.945

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions (P_{adjust} < 0 .05) and heterogeneity (Q_{pvalue} < 0.1) findings are in bold.

Table 55: Interaction between SFA subtypes and rs11126666 on BMI

	SCHS case			SCHS control			Meta-analysis				
	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	$Q_{p\text{-}value}$
perSatFA	-0.471	0.213	0.028	-0.147	0.171	0.390	-0.273	0.133	0.040	0.240	0.236
logc150perc	-0.056	0.190	0.771	-0.052	0.189	0.785	-0.054	0.134	0.690	1.000	0.988
logc160perc	0.450	0.587	0.444	-0.204	0.620	0.742	0.141	0.426	0.741	1.000	0.444
logc170perc	-0.447	0.322	0.165	-0.226	0.295	0.443	-0.327	0.217	0.133	1.000	0.613
logc180perc	-0.208	0.321	0.517	-0.124	0.347	0.722	-0.169	0.235	0.473	1.000	0.858
logc200perc	0.277	0.227	0.223	-0.043	0.251	0.863	0.133	0.168	0.430	1.000	0.344

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

Table 56: Interaction between 64 SNPs and %MFA intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	-0.093	0.060	0.121	0.011	0.046	0.807	-0.024	0.041	0.553	-0.028	0.046	0.537	-0.026	0.023	0.257	1.000	0.588	-0.015	0.025	0.564	1.000	0.794
2	rs1016287	0.091	0.063	0.151	-0.043	0.051	0.409	0.026	0.052	0.624	0.016	0.051	0.749	0.016	0.027	0.547	1.000	0.435	-3.23E-04	0.030	0.991	1.000	0.599
3	rs10182181	0.039	0.060	0.518	0.042	0.043	0.321	-0.019	0.043	0.654	-0.087	0.047	0.062	-0.009	0.023	0.704	1.000	0.176	-0.018	0.026	0.490	1.000	0.123
4	rs10733682	-0.006	0.070	0.935	-0.062	0.054	0.249	-0.025	0.047	0.600	0.061	0.054	0.264	-0.010	0.027	0.720	1.000	0.434	-0.011	0.030	0.723	1.000	0.255
5	rs10938397	0.042	0.065	0.514	-0.003	0.051	0.954	0.059	0.048	0.222	0.007	0.051	0.895	0.026	0.026	0.332	1.000	0.802	0.022	0.029	0.440	1.000	0.633
6	rs10968576	-0.065	0.074	0.383	0.009	0.057	0.868	-0.088	0.055	0.112	-0.074	0.060	0.214	-0.053	0.030	0.078	1.000	0.626	-0.051	0.033	0.123	1.000	0.423
7	rs11030104	0.012	0.057	0.830	-0.028	0.042	0.511	0.002	0.040	0.951	-0.042	0.047	0.368	-0.015	0.023	0.500	1.000	0.841	-0.020	0.025	0.409	1.000	0.755
8	rs11126666	-0.119	0.060	0.047	-0.029	0.049	0.554	-0.016	0.046	0.724	-0.085	0.050	0.087	-0.056	0.025	0.027	1.000	0.471	-0.042	0.028	0.132	1.000	0.564
9	rs11191560	0.052	0.064	0.415	0.061	0.050	0.222	0.015	0.049	0.761	-0.124	0.053	0.020	-3.34E-05	0.027	0.999	1.000	**0.054**	-0.011	0.029	0.707	1.000	**0.033**
10	rs11583200	0.081	0.087	0.357	-0.019	0.079	0.809	-0.005	0.080	0.953	0.009	0.094	0.921	0.014	0.042	0.742	1.000	0.847	-0.006	0.048	0.894	1.000	0.973
11	rs11688816	0.118	0.063	0.061	-0.113	0.046	0.015	-0.059	0.046	0.203	-0.025	0.050	0.621	-0.038	0.025	0.131	1.000	**0.028**	-0.067	0.027	0.014	1.000	0.415
12	rs12286929	0.034	0.067	0.612	0.014	0.048	0.769	-0.038	0.050	0.445	-0.117	0.050	0.020	-0.033	0.026	0.209	1.000	0.188	-0.045	0.028	0.114	1.000	0.165
13	rs12429545	-0.018	0.068	0.793	0.100	0.049	0.042	-0.056	0.048	0.250	0.089	0.053	0.093	0.032	0.027	0.223	1.000	**0.075**	0.041	0.029	0.151	1.000	**0.044**
14	rs12566985	0.007	0.072	0.919	0.112	0.057	0.051	-0.054	0.057	0.339	0.025	0.058	0.669	0.024	0.030	0.435	1.000	0.231	0.027	0.033	0.416	1.000	0.120
15	rs12940622	-0.107	0.060	0.077	-0.053	0.049	0.279	0.003	0.045	0.954	-0.052	0.050	0.297	-0.045	0.025	0.075	1.000	0.526	-0.032	0.028	0.250	1.000	0.623
16	rs13021737	-0.139	0.123	0.257	-0.046	0.087	0.599	0.004	0.074	0.962	-0.037	0.100	0.714	-0.038	0.046	0.403	1.000	0.802	-0.022	0.049	0.655	1.000	0.899
17	rs13201877	0.282	0.196	0.151	-0.095	0.101	0.347	0.096	0.104	0.354	-0.008	0.105	0.940	0.020	0.057	0.724	1.000	0.296	-0.004	0.059	0.946	1.000	0.418
18	rs1441264	0.016	0.062	0.797	-0.018	0.046	0.701	0.053	0.042	0.203	0.014	0.046	0.768	0.018	0.024	0.438	1.000	0.724	0.019	0.026	0.463	1.000	0.517
19	rs1460676	-0.036	0.059	0.541	0.065	0.045	0.147	0.061	0.042	0.142	-0.002	0.046	0.957	0.031	0.023	0.190	1.000	0.403	0.043	0.026	0.090	1.000	0.495
20	rs1516725	-0.048	0.106	0.650	-0.100	0.086	0.246	0.113	0.071	0.111	-0.036	0.089	0.685	2.97E-04	0.043	0.994	1.000	0.235	0.010	0.047	0.836	1.000	0.135
21	rs1528435	-0.098	0.063	0.123	-0.093	0.045	0.038	-0.031	0.045	0.487	0.013	0.046	0.778	-0.047	0.024	0.053	1.000	0.317	-0.038	0.026	0.145	1.000	0.250
22	rs1558902	0.031	0.088	0.720	0.055	0.064	0.385	-0.043	0.066	0.513	-0.072	0.069	0.295	-0.009	0.035	0.797	1.000	0.504	-0.017	0.038	0.662	1.000	0.352
23	rs16851483	-0.035	0.064	0.589	-0.003	0.052	0.950	0.015	0.046	0.748	-0.039	0.053	0.467	-0.011	0.026	0.666	1.000	0.864	-0.007	0.029	0.819	1.000	0.747

Table 56 (continued): Interaction between 64 SNPs and %MFA intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	0.067	0.059	0.262	0.002	0.043	0.959	0.032	0.043	0.460	0.038	0.047	0.419	0.030	0.023	0.201	1.000	0.842	0.023	0.026	0.364	1.000	0.828
25	rs17203016	-0.062	0.088	0.481	-0.089	0.062	0.150	0.015	0.060	0.808	0.008	0.069	0.911	-0.029	0.034	0.388	1.000	0.595	-0.023	0.037	0.521	1.000	0.421
26	rs17405819	-0.083	0.061	0.171	-0.036	0.045	0.422	-0.024	0.042	0.577	0.023	0.047	0.625	-0.024	0.024	0.307	1.000	0.566	-0.014	0.026	0.598	1.000	0.632
27	rs17724992	-0.053	0.059	0.371	-0.006	0.044	0.893	-0.044	0.040	0.272	0.010	0.047	0.829	-0.022	0.023	0.346	1.000	0.757	-0.016	0.025	0.519	1.000	0.652
28	rs1928295	-0.037	0.058	0.525	-0.014	0.045	0.761	0.003	0.041	0.940	-0.047	0.047	0.317	-0.020	0.023	0.388	1.000	0.859	-0.017	0.025	0.507	1.000	0.719
29	rs2033529	-0.147	0.081	0.069	-0.007	0.061	0.912	-0.087	0.053	0.099	-2.07E-05	0.062	1.000	-0.054	0.031	0.084	1.000	0.380	-0.037	0.034	0.265	1.000	0.473
30	rs2033732	1.48E-04	0.058	0.998	-0.083	0.046	0.070	0.015	0.042	0.713	0.019	0.047	0.690	-0.012	0.024	0.600	1.000	0.345	-0.015	0.026	0.565	1.000	0.196
31	rs205262	-0.028	0.078	0.723	0.160	0.060	0.008	0.125	0.062	0.044	0.121	0.065	0.062	0.108	0.033	0.001	0.074	0.277	0.136	0.036	1.47E-04	0.011	0.881
32	rs2075650	0.064	0.101	0.526	-0.005	0.083	0.956	-0.040	0.075	0.596	-0.042	0.087	0.631	-0.013	0.043	0.767	1.000	0.843	-0.029	0.047	0.534	1.000	0.938
33	rs2080454	0.015	0.059	0.793	0.010	0.044	0.818	-0.018	0.042	0.676	-0.003	0.045	0.946	-0.001	0.023	0.969	1.000	0.960	-0.004	0.025	0.876	1.000	0.901
34	rs2112347	-0.029	0.055	0.598	0.044	0.044	0.326	0.030	0.042	0.464	-0.002	0.049	0.964	0.016	0.023	0.494	1.000	0.725	0.026	0.026	0.315	1.000	0.779
35	rs2176040	-0.152	0.114	0.183	-0.107	0.083	0.198	0.076	0.082	0.358	-0.165	0.09	0.069	-0.073	0.045	0.103	1.000	0.175	-0.059	0.049	0.230	1.000	0.111
36	rs2207139	0.012	0.079	0.883	0.002	0.064	0.974	0.078	0.062	0.214	0.008	0.068	0.908	0.027	0.034	0.419	1.000	0.818	0.031	0.037	0.410	1.000	0.643
37	rs2287019	0.169	0.074	0.022	0.070	0.055	0.200	-0.051	0.051	0.316	-0.047	0.063	0.452	0.020	0.029	0.501	1.000	**0.046**	-0.008	0.032	0.792	1.000	0.208
38	rs2365389	-0.035	0.081	0.665	-0.060	0.060	0.315	0.085	0.065	0.190	0.024	0.069	0.728	0.004	0.034	0.912	1.000	0.387	0.012	0.037	0.748	1.000	0.253
39	rs2820292	0.009	0.067	0.895	0.012	0.057	0.832	0.040	0.051	0.437	-0.024	0.057	0.678	0.011	0.029	0.694	1.000	0.877	0.012	0.032	0.710	1.000	0.711
40	rs2836754	0.035	0.060	0.562	-0.026	0.045	0.569	-0.120	0.042	0.004	0.019	0.049	0.700	-0.036	0.024	0.134	1.000	**0.083**	-0.049	0.026	0.060	1.000	**0.081**
41	rs29941	0.142	0.075	0.059	0.082	0.053	0.122	-0.028	0.051	0.578	-0.073	0.056	0.191	0.016	0.029	0.566	1.000	**0.053**	-0.005	0.031	0.874	1.000	0.112
42	rs3101336	-0.049	0.101	0.630	-0.185	0.085	0.030	-0.072	0.069	0.300	0.018	0.092	0.841	-0.076	0.042	0.070	1.000	0.427	-0.082	0.046	0.076	1.000	0.261
43	rs3817334	0.002	0.062	0.979	-0.059	0.050	0.233	0.012	0.048	0.801	-0.032	0.051	0.528	-0.021	0.026	0.426	1.000	0.741	-0.025	0.029	0.375	1.000	0.578
44	rs3849570	0.017	0.059	0.772	-0.039	0.044	0.376	0.059	0.041	0.149	-0.048	0.047	0.305	-0.001	0.023	0.963	1.000	0.261	-0.004	0.025	0.862	1.000	0.143
45	rs3888190	-0.090	0.109	0.412	0.048	0.084	0.571	0.115	0.073	0.117	0.010	0.082	0.905	0.040	0.042	0.349	1.000	0.458	0.062	0.046	0.174	1.000	0.621
46	rs4256980	0.024	0.063	0.705	0.036	0.044	0.411	0.103	0.043	0.018	0.001	0.047	0.984	0.045	0.024	0.058	1.000	0.418	0.049	0.026	0.058	1.000	0.259

Table 56 (continued): Interaction between 64 SNPs and %MFA intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	0.058	0.063	0.360	0.076	0.052	0.143	0.007	0.049	0.886	0.044	0.055	0.427	0.044	0.027	0.104	1.000	0.802	0.041	0.030	0.173	1.000	0.625
48	rs4787491	-0.066	0.059	0.266	-3.62E-04	0.043	0.993	-0.015	0.041	0.724	-0.071	0.046	0.124	-0.032	0.023	0.162	1.000	0.620	-0.026	0.025	0.294	1.000	0.498
49	rs492400	0.049	0.073	0.502	-0.005	0.054	0.925	-0.026	0.050	0.606	0.092	0.055	0.095	0.022	0.028	0.443	1.000	0.404	0.017	0.030	0.582	1.000	0.252
50	rs6567160	0.071	0.078	0.367	0.023	0.060	0.700	-0.074	0.055	0.182	0.023	0.062	0.709	-2.29E-04	0.031	0.994	1.000	0.410	-0.014	0.034	0.690	1.000	0.385
51	rs6804842	-0.024	0.062	0.704	0.048	0.045	0.288	-0.011	0.045	0.803	0.025	0.048	0.603	0.013	0.024	0.581	1.000	0.728	0.020	0.027	0.446	1.000	0.643
52	rs7138803	-0.065	0.065	0.321	0.043	0.051	0.400	-0.097	0.046	0.036	0.006	0.054	0.918	-0.029	0.026	0.263	1.000	0.181	-0.023	0.029	0.433	1.000	0.104
53	rs7141420	-0.033	0.060	0.581	-0.004	0.044	0.919	-0.016	0.042	0.704	-0.044	0.045	0.336	-0.023	0.023	0.331	1.000	0.931	-0.021	0.025	0.411	1.000	0.815
54	rs7164727	-0.138	0.071	0.052	0.001	0.049	0.990	0.051	0.048	0.289	-0.081	0.052	0.121	-0.025	0.027	0.353	1.000	**0.091**	-0.006	0.029	0.831	1.000	0.174
55	rs7239883	0.021	0.063	0.740	-0.018	0.048	0.703	0.006	0.045	0.897	-0.066	0.050	0.186	-0.017	0.025	0.508	1.000	0.663	-0.024	0.027	0.385	1.000	0.561
56	rs7243357	-0.143	0.068	0.037	-0.019	0.053	0.725	0.078	0.058	0.177	-0.085	0.057	0.134	-0.034	0.029	0.239	1.000	**0.066**	-0.010	0.032	0.754	1.000	0.129
57	rs7599312	0.026	0.207	0.898	0.024	0.179	0.893	0.108	0.113	0.340	0.030	0.167	0.859	0.065	0.077	0.403	1.000	0.965	0.071	0.083	0.395	1.000	0.889
58	rs7715256	0.007	0.147	0.963	0.050	0.129	0.701	-0.103	0.106	0.334	-0.085	0.117	0.467	-0.045	0.061	0.463	1.000	0.783	-0.056	0.067	0.407	1.000	0.630
59	rs7903146	-0.154	0.242	0.525	-0.082	0.126	0.517	0.455	0.198	0.022	0.017	0.166	0.917	0.031	0.084	0.710	1.000	0.114	0.057	0.090	0.528	1.000	**0.071**
60	rs9374842	-0.111	0.119	0.352	0.045	0.077	0.562	0.026	0.080	0.745	0.028	0.079	0.724	0.015	0.043	0.727	1.000	0.726	0.033	0.046	0.465	1.000	0.983
61	rs9400239	0.043	0.064	0.501	0.009	0.046	0.843	-0.005	0.046	0.915	-0.089	0.050	0.078	-0.014	0.025	0.568	1.000	0.348	-0.025	0.027	0.366	1.000	0.309
62	rs9641123	-0.019	0.062	0.764	0.022	0.047	0.630	0.012	0.045	0.789	-0.032	0.050	0.525	-0.001	0.025	0.973	1.000	0.850	0.003	0.027	0.925	1.000	0.705
63	rs977747	0.045	0.176	0.798	0.268	0.119	0.025	0.040	0.118	0.735	-0.014	0.095	0.884	0.076	0.059	0.199	1.000	0.306	0.080	0.063	0.203	1.000	0.167
64	rs9914578	0.006	0.074	0.935	0.055	0.054	0.307	0.009	0.052	0.861	-0.054	0.061	0.370	0.007	0.029	0.800	1.000	0.610	0.008	0.032	0.810	1.000	0.402

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions ($P_{adjust} < 0$ .05) and heterogeneity ($Q_{pvalue} < 0.1$) findings are in bold.

6.3.7.9 %PFA

Table 57 shows the interaction results between 64 SNPs and %PFA intake on Z-BMI. None of the interaction remained statistically significant after adjusting for multiple testing. Nominal significant SNP × %PFA interaction on BMI was observed for *BDNF* rs11030104 (β=-0.069, SE=0.023, $P_{interaction}$=0.002), *C6orf106* rs205262 (β=0.072, SE=0.033, $P_{interaction}$= 0.029), *LOC646736* rs2176040 (β=-0.099, SE=0.045, $P_{interaction}$=0.028) and *NEGR1* rs3101336 (β=-0.131 SE=0.044, $P_{interaction}$= 0.003). In the case of rs205262, BMI level increased as the number of G allele and the intake of %PFA increased while for the rest SNPs, BMI level decreased as the number of reported BMI risk alleles and the intake of %PFA increased.

6.3.7.10 %Carbohydrate

Table 58 shows the interaction results between 64 SNPs and %Carbohydrate intake on Z-BMI. None of the interaction remained statistically significant after correction for multiple comparisons. Nominal significant SNP × %Carbohydrate interaction on BMI was observed for *LINGO2* rs10968576 (β=0.076, SE=0.030, $P_{interaction}$= 0.013), *RPTOR* rs12940622 (β=0.055, SE=0.025, $P_{interaction}$= 0.026), *TDRG1* rs2033529 (β=0.063, SE=0.031, $P_{interaction}$= 0.042), *C6orf106* rs205262 (β=-0.107, SE=0.033, $P_{interaction}$= 0.001) and *MTCH2* rs3817334 (β=0.054, SE=0.026, $P_{interaction}$=0.041). In the case of rs205262, BMI level decreased as the number of G allele and the intake of %Carbohydrate increased while for the rest SNPs, BMI level increased as the number of reported BMI risk alleles and the intake of %Carbohydrate increased.

Table 57: Interaction between 64 SNPs and %PFA intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	-0.033	0.059	0.583	-0.022	0.044	0.622	0.043	0.042	0.311	-0.058	0.046	0.212	-0.013	0.023	0.586	1.000	0.418	-0.009	0.025	0.721	1.000	0.259
2	rs1016287	-0.001	0.064	0.989	-0.033	0.047	0.485	0.043	0.048	0.378	-0.023	0.052	0.658	-0.004	0.026	0.892	1.000	0.695	-0.004	0.028	0.887	1.000	0.486
3	rs10182181	0.030	0.060	0.620	0.029	0.044	0.507	-0.051	0.044	0.248	0.026	0.045	0.557	0.006	0.024	0.808	1.000	0.511	0.001	0.026	0.958	1.000	0.346
4	rs10733682	-0.094	0.065	0.146	0.031	0.051	0.547	-0.049	0.051	0.337	0.084	0.056	0.135	-0.002	0.027	0.938	1.000	0.130	0.018	0.030	0.553	1.000	0.204
5	rs10938397	-0.055	0.068	0.422	0.006	0.048	0.893	0.042	0.047	0.377	0.118	0.052	0.023	0.036	0.026	0.164	1.000	0.198	0.052	0.028	0.066	1.000	0.276
6	rs10968576	0.043	0.079	0.590	0.049	0.058	0.402	-0.087	0.054	0.105	-0.035	0.060	0.558	-0.017	0.030	0.571	1.000	0.302	-0.028	0.033	0.401	1.000	0.227
7	rs11030104	-0.080	0.057	0.163	-0.075	0.042	0.074	-0.058	0.041	0.161	-0.069	0.045	0.124	-0.069	0.023	0.002	0.148	0.989	-0.067	0.025	0.006	0.444	0.958
8	rs11126666	-0.063	0.061	0.301	-0.014	0.046	0.767	0.069	0.047	0.144	-0.051	0.050	0.301	-0.008	0.025	0.745	1.000	0.235	0.003	0.027	0.913	1.000	0.193
9	rs11191560	-0.008	0.070	0.910	0.031	0.048	0.518	0.010	0.047	0.822	-0.065	0.053	0.221	-0.004	0.026	0.869	1.000	0.582	-0.004	0.028	0.896	1.000	0.377
10	rs11583200	0.120	0.106	0.260	0.010	0.076	0.894	-0.037	0.078	0.637	0.044	0.091	0.630	0.021	0.043	0.621	1.000	0.682	0.002	0.047	0.964	1.000	0.791
11	rs11688816	0.010	0.066	0.877	-0.117	0.049	0.018	-0.010	0.045	0.817	0.001	0.048	0.978	-0.032	0.025	0.204	1.000	0.249	-0.039	0.027	0.150	1.000	0.162
12	rs12286929	0.012	0.066	0.850	0.043	0.051	0.394	0.005	0.048	0.915	0.058	0.050	0.244	0.031	0.026	0.235	1.000	0.869	0.035	0.029	0.226	1.000	0.732
13	rs12429545	0.021	0.067	0.753	0.041	0.050	0.413	0.014	0.047	0.765	0.026	0.055	0.630	0.026	0.027	0.334	1.000	0.984	0.027	0.029	0.359	1.000	0.927
14	rs12566985	-0.022	0.076	0.776	0.085	0.057	0.133	0.038	0.056	0.500	-0.036	0.064	0.574	0.025	0.031	0.421	1.000	0.482	0.034	0.034	0.314	1.000	0.365
15	rs12940622	-0.098	0.061	0.111	0.010	0.047	0.831	-0.034	0.045	0.453	0.007	0.048	0.882	-0.022	0.025	0.386	1.000	0.489	-0.007	0.027	0.808	1.000	0.751
16	rs13021737	-0.233	0.119	0.051	-0.067	0.088	0.444	-0.002	0.080	0.979	-0.051	0.104	0.622	-0.067	0.047	0.154	1.000	0.452	-0.036	0.051	0.479	1.000	0.849
17	rs13201877	0.095	0.198	0.632	-0.114	0.109	0.297	-0.078	0.107	0.466	-0.108	0.110	0.327	-0.082	0.060	0.171	1.000	0.816	-0.100	0.063	0.112	1.000	0.970
18	rs1441264	-0.009	0.058	0.881	-0.017	0.045	0.702	0.010	0.042	0.813	0.008	0.045	0.853	-0.001	0.023	0.975	1.000	0.968	0.001	0.025	0.975	1.000	0.889
19	rs1460676	0.026	0.059	0.659	0.052	0.047	0.263	-0.014	0.041	0.729	0.021	0.047	0.659	0.018	0.024	0.442	1.000	0.759	0.017	0.026	0.518	1.000	0.562
20	rs1516725	-0.020	0.119	0.864	-0.070	0.088	0.424	-0.014	0.074	0.848	-0.098	0.090	0.278	-0.050	0.044	0.264	1.000	0.888	-0.054	0.048	0.256	1.000	0.754
21	rs1528435	-0.028	0.066	0.667	-0.059	0.045	0.191	-0.017	0.044	0.708	0.082	0.049	0.095	-0.006	0.025	0.804	1.000	0.190	-0.003	0.027	0.925	1.000	**0.099**
22	rs1558902	0.171	0.083	0.039	0.037	0.065	0.576	-0.049	0.066	0.452	-0.009	0.077	0.903	0.026	0.036	0.465	1.000	0.201	-0.007	0.040	0.859	1.000	0.650
23	rs16851483	-0.019	0.064	0.772	0.024	0.050	0.624	0.051	0.047	0.269	-0.067	0.051	0.188	0.002	0.026	0.932	1.000	0.351	0.006	0.028	0.825	1.000	0.207

Table 57 (continued): Interaction between 64 SNPs and %PFA intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
24	rs16951275	-4.70E-04	0.064	0.994	0.012	0.043	0.780	-0.006	0.044	0.887	-0.059	0.047	0.208	-0.013	0.024	0.570	1.000	0.713	-0.016	0.026	0.543	1.000	0.517
25	rs17203016	-0.012	0.084	0.888	0.003	0.062	0.967	-0.021	0.062	0.734	0.052	0.065	0.424	0.006	0.033	0.848	1.000	0.864	0.010	0.036	0.787	1.000	0.710
26	rs17405819	0.005	0.059	0.933	0.008	0.044	0.862	-0.058	0.042	0.165	-0.009	0.046	0.839	-0.017	0.023	0.454	1.000	0.694	-0.021	0.025	0.395	1.000	0.528
27	rs17724992	-0.096	0.057	0.094	0.019	0.044	0.657	0.001	0.04	0.986	0.041	0.045	0.366	0.001	0.023	0.976	1.000	0.280	0.019	0.025	0.442	1.000	0.809
28	rs1928295	0.001	0.056	0.989	0.059	0.045	0.189	0.045	0.04	0.276	2.25E-04	0.046	0.996	0.030	0.023	0.195	1.000	0.743	0.036	0.025	0.158	1.000	0.631
29	rs2033529	-0.073	0.085	0.395	0.032	0.061	0.602	-0.071	0.05	0.173	0.052	0.059	0.382	-0.012	0.031	0.695	1.000	0.326	-0.003	0.033	0.928	1.000	0.236
30	rs2033732	-0.031	0.056	0.583	0.019	0.045	0.679	-0.025	0.04	0.545	-0.068	0.045	0.134	-0.026	0.023	0.265	1.000	0.605	-0.025	0.025	0.329	1.000	0.400
31	rs205262	-0.004	0.080	0.958	0.152	0.061	0.013	0.084	0.06	0.183	0.019	0.066	0.777	0.072	0.033	0.029	1.000	0.342	0.088	0.037	0.015	1.000	0.329
32	rs2075650	-0.006	0.100	0.949	0.015	0.092	0.868	-0.019	0.07	0.813	0.002	0.081	0.984	-0.003	0.043	0.945	1.000	0.994	-0.002	0.048	0.963	1.000	0.960
33	rs2080454	0.048	0.059	0.417	-0.016	0.045	0.730	0.092	0.04	0.025	-0.025	0.046	0.590	0.027	0.023	0.251	1.000	0.186	0.023	0.025	0.368	1.000	**0.098**
34	rs2112347	-0.076	0.058	0.186	0.073	0.045	0.100	-0.026	0.04	0.541	-0.033	0.046	0.474	-0.009	0.023	0.708	1.000	0.157	0.004	0.025	0.862	1.000	0.168
35	rs2176040	-0.017	0.113	0.880	-0.196	0.091	0.032	0.004	0.08	0.963	-0.165	0.083	0.046	-0.099	0.045	0.028	1.000	0.280	-0.114	0.049	0.020	1.000	0.201
36	rs2207139	-0.075	0.075	0.317	-0.026	0.061	0.675	0.087	0.06	0.164	0.085	0.072	0.242	0.020	0.033	0.541	1.000	0.249	0.044	0.037	0.238	1.000	0.351
37	rs2287019	0.067	0.073	0.359	0.068	0.057	0.231	-0.036	0.05	0.484	-0.091	0.063	0.147	-0.003	0.030	0.928	1.000	0.181	-0.016	0.032	0.611	1.000	0.151
38	rs2365389	-0.108	0.080	0.178	-0.048	0.060	0.429	-0.006	0.06	0.932	0.031	0.070	0.659	-0.029	0.034	0.398	1.000	0.587	-0.011	0.037	0.760	1.000	0.692
39	rs2820292	0.043	0.066	0.513	0.062	0.059	0.293	-0.044	0.05	0.391	-0.028	0.058	0.620	0.002	0.029	0.941	1.000	0.474	-0.008	0.032	0.814	1.000	0.362
40	rs2836754	-0.023	0.058	0.692	0.021	0.044	0.626	-0.011	0.04	0.791	0.017	0.048	0.725	0.003	0.023	0.901	1.000	0.902	0.008	0.026	0.756	1.000	0.846
41	rs29941	0.070	0.071	0.325	0.042	0.053	0.426	-0.045	0.05	0.421	-4.35E-04	0.057	0.994	0.012	0.029	0.674	1.000	0.557	0.001	0.032	0.986	1.000	0.527
42	rs3101336	-0.143	0.114	0.209	-0.245	0.082	0.003	-0.044	0.07	0.567	-0.108	0.089	0.228	-0.131	0.044	0.003	1.000	0.355	-0.129	0.048	0.007	0.518	0.198
43	rs3817334	-0.012	0.062	0.850	-0.059	0.047	0.212	-0.043	0.04	0.373	-0.052	0.049	0.289	-0.045	0.025	0.078	1.000	0.941	-0.051	0.028	0.065	1.000	0.970
44	rs3849570	-0.005	0.061	0.936	-0.053	0.043	0.219	0.014	0.04	0.730	-0.102	0.050	0.042	-0.035	0.024	0.142	1.000	0.302	-0.040	0.026	0.119	1.000	0.186
45	rs3888190	-0.062	0.104	0.554	0.063	0.080	0.433	0.070	0.07	0.353	0.077	0.075	0.305	0.050	0.041	0.219	1.000	0.712	0.070	0.044	0.113	1.000	0.992
46	rs4256980	0.030	0.063	0.632	0.014	0.044	0.744	-0.006	0.04	0.895	0.021	0.045	0.642	0.012	0.023	0.601	1.000	0.961	0.009	0.025	0.710	1.000	0.904

Table 57 (continued): Interaction between 64 SNPs and %PFA intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	0.051	0.066	0.437	0.011	0.050	0.829	-0.007	0.048	0.884	0.014	0.056	0.801	0.013	0.027	0.637	1.000	0.916	0.005	0.029	0.866	1.000	0.950
48	rs4787491	-0.142	0.059	0.017	-0.001	0.043	0.982	0.038	0.044	0.380	-0.066	0.046	0.150	-0.029	0.023	0.221	1.000	**0.070**	-0.008	0.025	0.760	1.000	0.252
49	rs492400	0.047	0.079	0.547	0.004	0.054	0.936	0.013	0.051	0.800	0.010	0.057	0.864	0.014	0.029	0.621	1.000	0.974	0.009	0.031	0.769	1.000	0.993
50	rs6567160	0.043	0.077	0.577	0.050	0.055	0.366	-0.036	0.057	0.529	0.047	0.063	0.450	0.023	0.031	0.450	1.000	0.676	0.019	0.033	0.562	1.000	0.484
51	rs6804842	0.043	0.061	0.480	0.024	0.045	0.592	0.012	0.044	0.794	-0.080	0.048	0.092	-0.004	0.024	0.882	1.000	0.299	-0.012	0.026	0.641	1.000	0.225
52	rs7138803	-0.038	0.065	0.565	-0.040	0.050	0.419	-0.064	0.047	0.174	-0.026	0.053	0.621	-0.044	0.026	0.096	1.000	0.958	-0.045	0.029	0.117	1.000	0.861
53	rs7141420	0.001	0.059	0.989	-0.015	0.044	0.731	-0.046	0.042	0.269	-0.051	0.048	0.284	-0.031	0.023	0.185	1.000	0.865	-0.037	0.026	0.147	1.000	0.824
54	rs7164727	0.079	0.065	0.225	-0.026	0.048	0.588	0.053	0.050	0.293	0.098	0.052	0.057	0.045	0.026	0.086	1.000	0.315	0.039	0.029	0.179	1.000	0.199
55	rs7239883	-0.003	0.059	0.965	0.022	0.047	0.640	0.015	0.043	0.736	-0.054	0.049	0.277	-0.003	0.024	0.904	1.000	0.681	-0.003	0.027	0.910	1.000	0.471
56	rs7243357	-0.107	0.068	0.115	-0.030	0.055	0.584	-0.047	0.056	0.403	-0.030	0.055	0.583	-0.049	0.029	0.092	1.000	0.810	-0.036	0.032	0.265	1.000	0.970
57	rs7599312	0.155	0.196	0.429	0.267	0.181	0.140	-0.124	0.140	0.377	0.100	0.144	0.487	0.069	0.080	0.390	1.000	0.343	0.052	0.088	0.557	1.000	0.212
58	rs7715256	0.114	0.178	0.519	0.058	0.114	0.613	0.011	0.113	0.920	-0.146	0.135	0.278	0.004	0.064	0.954	1.000	0.602	-0.013	0.069	0.851	1.000	0.494
59	rs7903146	-0.188	0.204	0.359	0.041	0.150	0.787	0.013	0.147	0.927	-0.082	0.183	0.656	-0.031	0.083	0.709	1.000	0.806	-2.74E-05	0.091	1.000	1.000	0.869
60	rs9374842	0.029	0.113	0.798	0.004	0.074	0.961	-0.045	0.077	0.560	0.058	0.088	0.512	0.005	0.042	0.905	1.000	0.844	0.001	0.046	0.980	1.000	0.680
61	rs9400239	0.008	0.064	0.895	-0.021	0.046	0.647	-0.013	0.045	0.772	-0.037	0.050	0.461	-0.018	0.025	0.469	1.000	0.954	-0.023	0.027	0.401	1.000	0.936
62	rs9641123	-0.058	0.061	0.346	0.106	0.046	0.021	0.019	0.045	0.674	-0.010	0.048	0.843	0.024	0.024	0.320	1.000	0.139	0.040	0.027	0.135	1.000	0.186
63	rs977747	-0.086	0.160	0.591	0.081	0.126	0.522	0.060	0.116	0.604	-0.152	0.106	0.153	-0.027	0.061	0.654	1.000	0.422	-0.017	0.067	0.794	1.000	0.265
64	rs9914578	0.124	0.073	0.090	0.049	0.053	0.355	0.025	0.053	0.637	-0.079	0.058	0.173	0.022	0.029	0.448	1.000	0.154	0.003	0.032	0.930	1.000	0.231

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions (P_{adjust} < 0 .05) and heterogeneity (Q_{pvalue} < 0.1) findings are in bold.

Table 58: Interaction between 64 SNPs and %Carbohydrate intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
1	rs1000940	0.119	0.060	0.048	0.034	0.046	0.462	-0.017	0.042	0.686	0.092	0.046	0.045	0.046	0.024	0.050	1.000	0.185	0.033	0.026	0.199	1.000	0.213
2	rs1016287	-0.090	0.065	0.171	0.027	0.051	0.593	0.058	0.052	0.260	0.014	0.051	0.779	0.012	0.027	0.651	1.000	0.346	0.033	0.030	0.264	1.000	0.824
3	rs10182181	-0.046	0.059	0.439	-0.092	0.044	0.036	0.063	0.044	0.151	0.057	0.046	0.221	-0.001	0.024	0.972	1.000	**0.036**	0.008	0.026	0.766	1.000	**0.020**
4	rs10733682	0.047	0.070	0.503	0.053	0.055	0.330	0.040	0.047	0.397	-0.026	0.055	0.639	0.028	0.027	0.311	1.000	0.726	0.024	0.030	0.415	1.000	0.542
5	rs10938397	-0.053	0.066	0.422	0.060	0.052	0.250	-0.016	0.048	0.745	-0.028	0.052	0.585	-0.005	0.027	0.842	1.000	0.506	0.004	0.029	0.891	1.000	0.425
6	rs10968576	0.082	0.077	0.285	0.021	0.057	0.714	0.062	0.054	0.254	0.152	0.061	0.013	0.076	0.030	0.013	0.962	0.467	0.075	0.033	0.024	1.000	0.281
7	rs11030104	0.001	0.058	0.990	0.032	0.042	0.440	-0.047	0.041	0.251	0.056	0.046	0.217	0.009	0.023	0.694	1.000	0.350	0.010	0.025	0.673	1.000	0.196
8	rs11126666	0.118	0.060	0.049	0.003	0.047	0.956	-0.003	0.046	0.954	0.088	0.048	0.068	0.044	0.025	0.078	1.000	0.245	0.028	0.027	0.300	1.000	0.320
9	rs11191560	-0.061	0.064	0.342	-0.036	0.049	0.464	-0.060	0.046	0.195	0.089	0.053	0.095	-0.018	0.026	0.496	1.000	0.142	-0.009	0.029	0.748	1.000	**0.086**
10	rs11583200	-0.105	0.088	0.233	0.022	0.080	0.780	-0.025	0.078	0.751	-0.056	0.087	0.521	-0.037	0.041	0.372	1.000	0.749	-0.018	0.047	0.708	1.000	0.799
11	rs11688816	-0.043	0.062	0.485	0.057	0.046	0.212	0.034	0.045	0.455	-0.011	0.049	0.829	0.017	0.025	0.487	1.000	0.537	0.029	0.027	0.288	1.000	0.595
12	rs12286929	-0.004	0.066	0.946	1.98E-04	0.049	0.997	0.017	0.050	0.727	0.017	0.051	0.732	0.009	0.026	0.735	1.000	0.988	0.011	0.029	0.690	1.000	0.961
13	rs12429545	0.054	0.068	0.424	-0.089	0.047	0.058	-0.010	0.050	0.841	-0.106	0.052	0.040	-0.050	0.026	0.057	1.000	0.179	-0.068	0.028	0.017	1.000	0.345
14	rs12566985	0.003	0.075	0.963	-0.114	0.056	0.042	0.054	0.055	0.331	-0.002	0.060	0.979	-0.017	0.030	0.574	1.000	0.188	-0.021	0.033	0.526	1.000	**0.095**
15	rs12940622	0.134	0.059	0.023	0.062	0.047	0.192	0.029	0.044	0.511	0.023	0.051	0.650	0.055	0.025	0.026	1.000	0.466	0.038	0.027	0.162	1.000	0.827
16	rs13021737	0.129	0.126	0.305	0.095	0.087	0.280	0.006	0.079	0.936	0.105	0.097	0.281	0.071	0.047	0.127	1.000	0.785	0.062	0.050	0.218	1.000	0.663
17	rs13201877	-0.181	0.182	0.321	0.096	0.097	0.321	-0.155	0.103	0.131	0.081	0.111	0.465	-0.011	0.057	0.851	1.000	0.191	0.008	0.060	0.899	1.000	0.151
18	rs1441264	0.016	0.058	0.785	0.050	0.047	0.290	-0.105	0.042	0.013	0.017	0.047	0.718	-0.014	0.024	0.561	1.000	**0.065**	-0.020	0.026	0.446	1.000	**0.032**
19	rs1460676	0.092	0.062	0.138	0.024	0.045	0.598	-0.051	0.042	0.223	-0.012	0.046	0.787	4.68E-04	0.024	0.984	1.000	0.256	-0.015	0.025	0.555	1.000	0.475
20	rs1516725	0.110	0.122	0.367	0.162	0.087	0.063	-0.182	0.072	0.012	0.023	0.091	0.806	-0.007	0.044	0.878	1.000	**0.014**	-0.025	0.048	0.606	1.000	**0.008**
21	rs1528435	0.026	0.063	0.679	0.102	0.046	0.028	0.006	0.044	0.894	0.010	0.047	0.828	0.037	0.024	0.133	1.000	0.421	0.038	0.026	0.145	1.000	0.249
22	rs1558902	-0.022	0.085	0.794	-0.071	0.066	0.280	-0.033	0.066	0.615	0.057	0.073	0.434	-0.021	0.036	0.559	1.000	0.623	-0.021	0.039	0.601	1.000	0.414
23	rs16851483	0.042	0.065	0.521	0.019	0.052	0.715	-0.027	0.045	0.551	0.108	0.052	0.036	0.030	0.026	0.247	1.000	0.266	0.028	0.029	0.325	1.000	0.141

Table 58 (continued): Interaction between 64 SNPs and %Carbohydrate intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalu}
24	rs16951275	-0.016	0.058	0.787	0.044	0.043	0.308	-0.008	0.044	0.850	-0.035	0.046	0.448	-0.001	0.024	0.966	1.000	0.631	0.002	0.026	0.941	1.000	0.439
25	rs17203016	0.011	0.087	0.902	0.050	0.065	0.439	-0.023	0.059	0.696	-0.025	0.066	0.708	0.001	0.034	0.971	1.000	0.824	-4.30E-04	0.036	0.991	1.000	0.640
26	rs17405819	0.108	0.062	0.084	0.031	0.045	0.487	0.056	0.042	0.187	-0.053	0.048	0.269	0.029	0.024	0.221	1.000	0.175	0.016	0.026	0.545	1.000	0.214
27	rs17724992	0.088	0.060	0.146	0.018	0.043	0.668	0.045	0.041	0.265	-0.029	0.046	0.530	0.025	0.023	0.270	1.000	0.435	0.015	0.025	0.554	1.000	0.479
28	rs1928295	0.046	0.057	0.422	-0.002	0.044	0.958	-0.030	0.042	0.470	0.023	0.046	0.620	0.003	0.023	0.883	1.000	0.706	-0.005	0.025	0.844	1.000	0.693
29	rs2033529	0.138	0.078	0.079	0.074	0.060	0.216	0.043	0.055	0.440	0.031	0.062	0.618	0.063	0.031	0.042	1.000	0.717	0.049	0.034	0.147	1.000	0.872
30	rs2033732	0.028	0.057	0.627	0.041	0.046	0.379	0.009	0.042	0.838	0.024	0.046	0.606	0.024	0.024	0.306	1.000	0.965	0.023	0.026	0.366	1.000	0.875
31	rs205262	0.072	0.078	0.358	-0.163	0.062	0.008	-0.151	0.060	0.012	-0.119	0.068	0.079	-0.107	0.033	0.001	0.074	**0.083**	-0.146	0.036	**5.50E-05**	**0.004**	0.885
32	rs2075650	-0.027	0.106	0.798	-0.021	0.081	0.796	0.103	0.071	0.151	0.047	0.091	0.607	0.036	0.042	0.394	1.000	0.630	0.048	0.046	0.298	1.000	0.519
33	rs2080454	-0.027	0.060	0.651	-0.017	0.045	0.711	0.019	0.042	0.652	-0.009	0.046	0.841	-0.005	0.023	0.823	1.000	0.911	-0.001	0.025	0.960	1.000	0.828
34	rs2112347	0.004	0.057	0.941	0.015	0.045	0.738	-0.002	0.043	0.959	-0.006	0.048	0.906	0.003	0.024	0.904	1.000	0.989	0.003	0.026	0.922	1.000	0.942
35	rs2176040	0.168	0.111	0.130	0.072	0.093	0.441	-0.031	0.084	0.713	0.130	0.087	0.134	0.074	0.046	0.109	1.000	0.438	0.054	0.051	0.284	1.000	0.399
36	rs2207139	0.023	0.081	0.776	0.013	0.06	0.829	-0.075	0.064	0.240	0.054	0.069	0.428	3.94E-04	0.034	0.991	1.000	0.544	-0.004	0.037	0.907	1.000	0.360
37	rs2287019	-0.104	0.075	0.169	-0.130	0.055	0.019	0.020	0.053	0.711	0.023	0.061	0.706	-0.042	0.030	0.157	1.000	0.130	-0.031	0.033	0.344	1.000	**0.088**
38	rs2365389	0.021	0.083	0.798	-0.001	0.063	0.981	-0.056	0.065	0.387	-0.014	0.070	0.843	-0.016	0.034	0.641	1.000	0.888	-0.024	0.038	0.529	1.000	0.822
39	rs2820292	-0.031	0.066	0.637	0.006	0.056	0.908	0.016	0.052	0.764	0.011	0.061	0.852	0.003	0.029	0.913	1.000	0.951	0.011	0.032	0.725	1.000	0.993
40	rs2836754	-0.028	0.059	0.638	0.019	0.045	0.671	0.077	0.042	0.069	-0.018	0.050	0.715	0.021	0.024	0.374	1.000	0.384	0.031	0.026	0.237	1.000	0.329
41	rs29941	-0.140	0.075	0.062	-0.034	0.052	0.513	0.026	0.052	0.618	0.113	0.055	0.042	0.007	0.028	0.797	1.000	**0.041**	0.032	0.031	0.296	1.000	0.153
42	rs3101336	0.100	0.108	0.355	0.133	0.085	0.115	0.046	0.070	0.507	-0.047	0.092	0.610	0.057	0.043	0.183	1.000	0.518	0.049	0.046	0.293	1.000	0.354
43	rs3817334	-0.029	0.062	0.644	0.062	0.050	0.212	0.078	0.048	0.108	0.073	0.052	0.158	0.054	0.026	0.041	1.000	0.538	0.071	0.029	0.014	1.000	0.975
44	rs3849570	-0.021	0.058	0.724	0.057	0.043	0.190	-0.028	0.040	0.488	0.083	0.047	0.078	0.024	0.023	0.305	1.000	0.222	0.032	0.025	0.205	1.000	0.156
45	rs3888190	0.082	0.111	0.460	0.005	0.084	0.949	-0.137	0.073	0.061	0.005	0.078	0.954	-0.030	0.042	0.467	1.000	0.317	-0.049	0.045	0.278	1.000	0.311
46	rs4256980	-0.065	0.065	0.318	-0.037	0.044	0.404	-0.027	0.043	0.531	0.051	0.047	0.278	-0.015	0.024	0.539	1.000	0.409	-0.007	0.026	0.789	1.000	0.334

Table 58 (continued): Interaction between 64 SNPs and %Carbohydrate intake on BMI

	SNPs	SCHS case			SCHS control			SP2610			SP21m			SCHS + SP2610 + SP21m					SCHS control + SP2610 + SP21m				
		Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	Beta	SE	P	P_{adjust}	Q_{pvalue}	Beta	SE	P	P_{adjust}	Q_{pvalue}
47	rs4740619	-0.070	0.064	0.278	-0.065	0.052	0.210	-0.009	0.049	0.863	-0.041	0.054	0.449	-0.043	0.027	0.113	1.000	0.838	-0.037	0.030	0.214	1.000	0.728
48	rs4787491	0.133	0.060	0.027	0.021	0.043	0.624	-0.032	0.042	0.447	0.101	0.046	0.029	0.042	0.023	0.071	1.000	**0.064**	0.026	0.025	0.305	1.000	0.101
49	rs492400	-0.048	0.071	0.504	-0.007	0.052	0.892	-0.013	0.051	0.799	-0.070	0.055	0.206	-0.031	0.028	0.264	1.000	0.829	-0.028	0.031	0.353	1.000	0.663
50	rs6567160	-0.063	0.076	0.407	-0.009	0.058	0.875	0.052	0.053	0.327	-0.034	0.062	0.591	-0.004	0.030	0.908	1.000	0.582	0.008	0.033	0.814	1.000	0.543
51	rs6804842	0.034	0.063	0.584	-0.054	0.047	0.246	-0.003	0.044	0.938	0.027	0.048	0.578	-0.004	0.025	0.881	1.000	0.585	-0.011	0.027	0.692	1.000	0.471
52	rs7138803	0.023	0.067	0.737	-0.054	0.051	0.293	0.080	0.046	0.084	-0.011	0.054	0.838	0.013	0.027	0.627	1.000	0.260	0.011	0.029	0.701	1.000	0.136
53	rs7141420	-0.035	0.060	0.558	-0.005	0.044	0.911	0.039	0.043	0.358	0.039	0.044	0.377	0.016	0.023	0.495	1.000	0.678	0.025	0.025	0.326	1.000	0.714
54	rs7164727	0.047	0.070	0.497	0.015	0.050	0.768	-0.018	0.050	0.713	-0.031	0.052	0.545	-0.002	0.027	0.929	1.000	0.791	-0.011	0.029	0.701	1.000	0.802
55	rs7239883	-0.022	0.061	0.725	0.003	0.047	0.948	0.006	0.044	0.888	0.052	0.051	0.306	0.012	0.025	0.636	1.000	0.807	0.018	0.027	0.500	1.000	0.733
56	rs7243357	0.210	0.069	0.003	0.008	0.053	0.878	-0.049	0.059	0.406	0.046	0.057	0.422	0.040	0.029	0.175	1.000	**0.034**	0.003	0.032	0.928	1.000	0.509
57	rs7599312	-0.005	0.189	0.978	-0.056	0.163	0.731	0.022	0.120	0.856	0.070	0.164	0.669	0.011	0.076	0.888	1.000	0.957	0.014	0.083	0.868	1.000	0.858
58	rs7715256	-0.138	0.163	0.395	-0.231	0.134	0.085	0.076	0.106	0.476	0.081	0.111	0.464	-0.018	0.062	0.766	1.000	0.199	0.002	0.067	0.978	1.000	0.134
59	rs7903146	0.335	0.212	0.114	0.022	0.134	0.867	-0.339	0.175	0.053	0.106	0.168	0.530	0.009	0.083	0.911	1.000	**0.083**	-0.049	0.090	0.582	1.000	0.143
60	rs9374842	0.044	0.115	0.704	0.046	0.081	0.575	-0.029	0.071	0.680	0.064	0.077	0.406	0.026	0.041	0.534	1.000	0.818	0.023	0.044	0.603	1.000	0.637
61	rs9400239	-0.070	0.063	0.271	-0.003	0.046	0.947	-0.019	0.046	0.676	0.072	0.050	0.151	4.00E-04	0.025	0.987	1.000	0.326	0.014	0.027	0.622	1.000	0.368
62	rs9641123	-0.012	0.060	0.840	-0.058	0.046	0.212	0.018	0.044	0.686	-0.036	0.049	0.458	-0.022	0.024	0.374	1.000	0.677	-0.024	0.027	0.377	1.000	0.474
63	rs977747	0.099	0.185	0.592	-0.259	0.116	0.025	-0.029	0.123	0.810	0.064	0.104	0.539	-0.047	0.062	0.442	1.000	0.162	-0.066	0.065	0.315	1.000	0.109
64	rs9914578	-0.045	0.074	0.543	-0.059	0.053	0.270	-0.030	0.052	0.563	0.075	0.059	0.203	-0.016	0.029	0.589	1.000	0.354	-0.010	0.031	0.743	1.000	0.216

Q (Cochran's Q test) was used to measure between-study heterogeneity. Significant interactions (P_{adjust} < 0 .05) and heterogeneity (Q_{pvalue} < 0.1) findings are in bold.

In addition, if meta-analysis was conducted only in SCHS controls and SP2, the interaction between rs205262 and %Carbohydrate on Z-BMI would still be significant after correction for multiple testing (β=-0.146, SE=0.036, $P_{interaction}=5.05\times10^{-5}$, $P_{adjust}=0.004$).

6.4 Discussion

In this study, we investigated the association between diet and BMI, association between BMI risk loci and dietary components, and the interaction between dietary intake and BMI associated loci on BMI in 3,758 local Singaporean Chinese adults. This is the first study that systematically investigated the gene-environment interactions for established BMI-susceptibility loci in Asian populations thus far.

Most (84.38%) of the BMI susceptibility loci, although not statistically significant, showed directionally consistent association with BMI as reported previously [251]. Five loci (*GNPDA2*, *KCNK3*, *NT5C2*, *QPCTL* and *MC4R)* were significantly associated with the outcome and the most strongly associated locus was rs10938397 on *GNPDA2*.

Among the ten dietary components tested, total calories, cholesterol, starch, %protein, %fat, %MFA and %carbohydrate showed nominal significant association with BMI. After Bonferroni correction, only intake of total calories was significantly associated with the outcome. The increased intake of total calories

would increase individual's BMI level.

When the association between dietary components and 64 established BMI susceptibility loci was tested, it was found that the reported BMI risk allele G of rs6804842 on *RARB* would increase intake of total calories. Rs6804842 is an intronic variant on retinoic acid receptor beta (*RARB*), a member of the thyroid-steroid hormone receptor superfamily of nuclear transcriptional regulators. However, no studies have been published regarding the relationship between this loci and energy intake thus far.

Nominal evidence of interaction was observed between wGRS with %fat, %carbohydrate and starch intake on BMI. However, none of the interaction remained statistically significant after adjusting for multiple comparisons. When evaluated at single-SNP level, interaction analyses results revealed nominal significance for %fat × rs205262, cholesterol × rs4740619 and %SFA × rs11126666 on BMI. Rs205262 is an intronic SNP on chromosome 6 open reading frame 106 (*C6orf106*). Little has been known about this region so far. Previous findings showed that this region could promote the malignant progression of breast cancer and the specific SNP could interact with cigarette smoking on BMI [255, 268]. We have also tested the interaction in our Singaporean Chinese cohort and no significant interaction was observed. To find out the possible mechanism involved, HaploReg, a tool for exploring the annotations of the non-coding genome at variants on

haplotype blocks was used (http://www.broadinstitute.org/mammals/haploreg) and it is found that rs205262 might be able to affect the binding affinity of peroxisome proliferator-activated receptors (PPARs), a group of nuclear receptor proteins involved in regulation of cellular differentiation, development, and metabolism (carbohydrate, lipid, protein). *PPARs* are reported to be associated with obesity [269-271] and the association between genetic variants on *PPARs* and BMI could be modulated by dietary fat intake [272]. Thus the interaction between %fat and rs205262 on BMI might be through affecting the function of PPARs. Rs4740619 is an intronic variant on coiled-coil domain containing 171 (*CCDC171*), a newly identified gene on chromosome 9. Prediction result using HaploReg showed that rs4740619 could also affect the binding affinity of PPARs, as well as forkhead box P1 (FOXP1), a tumor suppressor. Rs11126666 is an intronic SNP on potassium two pore domain channel subfamily K member 3 (*KCNK3*). *KCNK3* has been reported to be associated with blood pressure and hypertension [273, 274]. Prediction result using HaploReg showed that rs11126666 could affect the binding affinity of upstream binding protein 1 (LBP-1), MYB proto-oncogene, transcription factor (MYB) and myogenic factor (MYF).

FTO, which is located on chromosome 16, has shown strongest association with BMI and obesity [110, 111]. Some studies have investigated the modification effect of dietary factors on the association between *FTO* variants and BMI. However, the results were controversial [36, 37, 258, 275-277]. In our Singaporean Chinese

cohorts, no such interactions were observed. One possible explanation for this is the modification effect of dietary factors on the association reported elsewhere might be population specific.

Some limitations of this study are as follow. Firstly, since the weight and height information in SCHS were self-reported via in-person interviews, a subset of individuals (16.92%) did not have measurements for both variables thus were not included in current analysis. This has significantly reduced the sample size. To increase the sample size and statistical power [278, 279], we are currently seeking additional cohorts to replicate and further confirm our results. Secondly, we used Hapmap imputation data for those SNPs without genotypes in the cohorts. Among the 97 reported BMI risk loci, only 64 (65.98%) exist in both SCHS and SP2. More SNPs might be captured if 1000 Genomes is used as the imputation panel. However, this is not available at the time of analysis.

In conclusion, the obesity risk SNPs are generally transferable between ethnic groups. Higher total calories intake is significantly associated with increased BMI in Singaporean Chinese population. Most known obesity risk loci did not show an association with dietary intake or interact with dietary intake to modify BMI levels. The association between rs205262 (*C6orf106*), rs11126666 (*KCNK3*) and rs4740619 (*CCDC171*) with BMI could be modified by %fat, %SFA and cholesterol intake, respectively.

Chapter 7: Interactions between high-density lipoprotein associated risk loci and SNPs across the genome on HDL levels and cholesterol ratio in Singaporean Chinese

7.1 Introduction

HDL is the smallest and densest lipoprotein particles, the protein to lipids proportion of which is highest among the five major lipoprotein groups. HDL plays a central role in reverse cholesterol transport pathway, which delivers excess cholesterol from arteries to the liver and then excreted into the bile [280]. Low concentration of HDL is strongly associated with accumulation of atherosclerosis within the arteries walls and eventually leads to increase risk of stroke, cardiovascular disease and vascular disease [40, 41]. Every 1 mg/dl decrease in HDL level will lead to a 6% increase in cardiovascular risk [42]. Thus HDL is sometimes referred to as 'good cholesterol' for its role in preventing atherosclerosis. Identifying risk factors that could affect HDL levels would be important in the diagnosis, treatment and prevention of heart disease [45].

Cholesterol ratio is the ratio between HDL and total cholesterol level in the plasma. Some researchers in recent years believe that lipoprotein ratios would be much more important in some aspects such as risk prediction for heart disease than the absolute lipoprotein levels [43]. Thus interest in cholesterol ratio has become another important subject of study in addition to absolute levels of HDL, TG, TC and LDL.

Recently, with the rapid development of large scale GWAS, many SNPs across the genome have been identified to be associated with blood HDL levels. However, the SNPs uncovered thus far could only explain a very small fraction of HDL variation [281, 282] despite the heritability of HDL was estimated to be up to 70% [283]. The large 'missing heritability' is believed to be due to variants that could not be captured by GWAS, such as rare variants and structure variants as well as due to gene-gene interactions and gene-environment interactions.

Gene-gene interaction, also called epistasis, is defined as 'deviation from additivity'. This is the phenomenon that the effect of one gene is dependent on the presence of the effect of other genes. The combined effect of epistatic mutations is usually different from the individual gene effect. Gene-gene interaction is believed to be partially responsible for the phenomenon that the same genetic polymorphism contributes differently to complex diseases in different environments or different genetic backgrounds. Thus it is suggested that gene-gene interaction is a ubiquitous part of the genetic architecture of complex disease [179]. Studying gene-gene interactions will help to better understand the etiology of complex diseases, including lipid metabolism and cardiovascular disease.

Several studies have explored gene-gene interaction for HDL levels using candidate gene approach. The SNPs studied were usually located on genes involved in HDL metabolic pathways. In addition, those studies were mainly conducted in European

ancestry populations [284-286]. Few studies are available in Asian populations that systemically investigated gene-gene interactions on HDL levels thus far. Our study attempts to explore the interactions between HDL associated risk loci from GWAS catalog [78] and independent SNPs across the genome for HDL levels and cholesterol ratio in Singaporean Chinese cohorts.

7.2 Method

7.2.1 Study Population

In total, 5,272 adult individuals from three independent Singaporean Chinese cohorts, the SCHS (N = 1,284), the SCES (N = 1,889) and the SP2 (N = 2,099) were included in the analysis. Since information for use of anti-hypertensive medication was not available in SCHS and the plasma lipid levels were usually abnormal for individuals with CHD, only healthy controls from SCHS were included in current study. All study subjects gave written informed consent. Detailed information regarding genotyping, quality control and lipid measurements in these three cohorts was described previously in chapter 3.

7.2.2 Candidate SNP selection

In GWAS catalog [78], 133 SNPs have been reported to be associated with HDL levels thus far. Among these 133 SNPs, 47 of them have been genotyped in all three cohorts (Table 59). These 47 SNPs were acted as the first set of SNPs in the analysis. The second set was SNPs across the whole genome. These SNPs were

Table 59: Single nucleotide polymorphisms includes in Set 1.

	SNP	Region	Position	Reported Gene(s)	Mapped_gene	RA/EA	RAF/EAF	P-value
1	rs4660293	1p34.3	39562508	*MACF1, PABPC4*	*PABPC4*	G	0.24	3.00E-18
2	rs12145743	1q23.1	156730859	*HDGF, PMVK*	*RRNAD1*	G	0.34	2.00E-08
3	rs6754295	2p24.1	20983311	*APOB*	*LOC101928271 - APOB*	C	0.25	4.00E-08
4	rs13326165	3p21.1	52498102	*STAB1*	*STAB1*	A	0.21	9.00E-11
5	rs2290547	3p21.31	47019693	*SETD2*	*SETD2*	A	0.20	4.00E-09
6	rs2602836	4q23	99093654	*ADH5*	*LOC100507053*	A	0.44	5.00E-08
7	rs2814944	6p21.31	34585020	*C6orf106*	*SPDEF - C6orf106*	A	0.16	4.00E-09
8	rs4917014	7p12.2	50266267	*IKZF1*	*C7orf72 - IKZF1*	G	0.32	1.00E-08
9	rs4731702	7q32.3	130748625	*KLF14*	*LOC105375508*	T	0.49	5.00E-17
10	rs17173637	7q36.1	150832361	*TMEM176A*	*AOC1, LOC105375567*	C	0.12	2.00E-08
11	rs12678919	8p21.3	19986711	*LPL*	*LPL - LOC105379311*	G	0.13	1.00E-149
12	rs2083637	8p21.3	20007664	*LPL*	*LPL - LOC105379311*	G	0.26	6.00E-18
13	rs12686004	9q31.1	104891145	*ABCA1*	*ABCA1*	T	0.21	2.00E-18
14	rs3905000	9q31.1	104894789	*ABCA1*	*ABCA1*	G	0.86	9.00E-13
15	rs4149268	9q31.1	104884939	*ABCA1*	*ABCA1*	C	0.64	1.00E-10
16	rs970548	10q11.21	45517829	*MARCH8, ALOX5*	*39508*	C	0.26	2.00E-10
17	rs11246602	11p11.12	54607190	*OR4C46*	*OR4C46 - OR4A4P*	C	0.15	2.00E-10
18	rs7120118	11p11.2	47264739	*NR1H3*	*NR1H3*	G	0.42	4.00E-08
19	rs7395662	11p11.2	48497341	*FOLH1, MADD*	*OR4A47 - OR4A45P*	G	0.61	6.00E-11
20	rs2923084	11p15.4	10367235	*AMPD3, ADM*	*CAND1.11*	G	0.18	5.00E-08
21	rs174546	11q12.2	61802358	*FADS1, FADS2, FADS3*	*FADS1*	T	0.36	8.00E-28
22	rs12801636	11q13.1	65623846	*KAT5*	*PCNXL3*	A	0.23	3.00E-08
23	rs964184	11q23.3	116778201	*APOA1, APOC3, APOA4, APOA5*	*LOC105369514 - ZPR1*	C	0.84	6.00E-48
24	rs7941030	11q24.1	122651667	*UBASH3B*	*GLULP3 - UBASH3B*	C	0.39	1.00E-14

Table 59 (continued): Single nucleotide polymorphisms includes in Set 1.

	SNP	Region	Position	Reported Gene(s)	Mapped_gene	RA/EA	RAF/EAF	P-value
25	rs7134375	12p12.2	20320824	*PDE3A*	*LOC105369688*	A	0.43	1.00E-08
26	rs7134594	12q24.11	109562388	*MVK, MMAB*	*MMAB*	C	0.48	2.00E-13
27	rs4983559	14q32.33	104810872	*ZBTB42, AKT1*	*ZBTB42 - LINC00638*	G	0.40	1.00E-08
28	rs10468017	15q21.3	58386313	*LIPC*	*LOC102724766*	T	0.30	8.00E-23
29	rs1532085	15q21.3	58391167	*LIPC*	*LOC102724766*	A	0.40	1.00E-188
30	rs12708980	16q13	56978467	*CETP*	*CETP*	C	0.10	2.00E-28
31	rs1532624	16q13	56971567	*CETP*	*CETP*	C	0.57	9.00E-94
32	rs1800775	16q13	56961324	*CETP*	*HERPUD1 - CETP*	A	0.49	4.00E-93
33	rs1864163	16q13	56963321	*CETP*	*CETP*	G	0.80	7.00E-39
34	rs3764261	16q13	56959412	*CETP*	*HERPUD1 - CETP*	A	0.32	1E-769
35	rs9989419	16q13	56951227	*CETP*	*HERPUD1 - CETP*	G	0.60	1.00E-32
36	rs2271293	16q22.1	67868167	*CTCF, PRMT8*	*NUTF2*	A	0.11	9.00E-13
37	rs255049	16q22.1	67979568	*LCAT*	*DPEP3*	G	0.22	3.00E-08
38	rs2925979	16q23.2	81501185	*CMIP*	*CMIP*	T	0.31	1.00E-19
39	rs4148008	17q24.2	68879153	*ABCA8*	*ABCA8*	G	0.33	1.00E-12
40	rs4129767	17q25.3	78407903	*PGS1*	*PGS1*	G	0.48	2.00E-11
41	rs4939883	18q21.1	49640844	*LIPG*	*LOC105372112*	G	0.83	2.00E-11
42	rs2278426	19p13.2	11239812	*TSPAN16, SPC24, RAB3D, KANK2, DOCK6, LOC55908*	*DOCK6, C19orf80*	?	0.30	3.00E-09
43	rs2967605	19p13.2	8404854	*ANGPTL4*	*RAB11B - MARCH2*	T	0.16	1.00E-08
44	rs737337	19p13.2	11236817	*DOCK6, LOC55908*	*DOCK6*	C	0.11	5.00E-17
45	rs17695224	19q13.41	51820963	*HAS1*	*FPR3, LOC105369197*	A	0.26	2.00E-13
46	rs1800961	20q13.12	44413724	*HNF4A*	*HNF4A*	T	0.05	2.00E-34
47	rs7679	20q13.12	45947863	*PLTP*	*PCIF1*	C	0.19	4.00E-09

RA: risk allele; EA: effect allele; RAF: risk allele frequency; EFA: effect allele frequency

pruned in ($r^2 < 0.10$) by PLINK version 1.07 independently in three cohorts. The number of overlapping SNPs is 74,409. Thus the threshold for significance in current study was 1.43×10^{-8} (P = 0.05/ (47×74,409)) after Bonferroni correction.

7.2.3 Statistical analysis

Quantitative variables were presented as mean ± SD while categorical variables were presented as number of individuals (percentage %). Age and HDL levels were not normally distributed thus differences between means of these two variables were evaluated by Kruskal-Wallis rank test. Plasma cholesterol level was normally distributed thus the difference of mean across cohorts were compared by one way analysis of variance (ANOVA). Differences in frequencies of categorical variables were evaluated by the chi square test. Cholesterol ratio was calculated as plasma HDL level divided by cholesterol level. HDL and cholesterol ratio were Z-score transformed before the analysis. Interaction analyses were first performed between 47 SNPs and 74,409 independent genome-wide SNPs in an additive model in PLINK version 1.07. Linear regression model was used by introducing the interaction term (SNP_1 x SNP_2) with the specific SNPs (SNP_1 and SNP_2) included as covariates. Analysis was carried out in each cohort individually and subsequently meta-analyzed using the inverse-variance weighted method in STATA (version 12.1, Statacorp, College Station, TX, USA). Those top hits were further analyzed by including additional covariates age, gender and anti-hyperlipidemia medication usage in the model in STATA. P value of 1.43×10^{-8} (2 tailed) was considered statistically

significant after adjusting for multiple comparison based on 3,497,223 tests (47×74,409). The power to detect the interactions was estimated by QUANTO (Version 1.2.4, Table 60).

Table 60: Power estimation of gene-gene interaction for HDL level/cholesterol ratio

Minor allele frequency of SNP_1	Minor allele frequency of SNP_2	Beta for SNP_1	Beta for SNP_2	Beta for interaction	Power
0.05	0.05	0.01	0.01	0.10	46.23%
				0.15	79.92%
				0.20	96.19%
				0.25	99.66%
		0.02	0.02	0.10	46.25%
				0.15	79.95%
				0.20	96.21%
				0.25	99.67%
		0.03	0.03	0.10	46.29%
				0.15	79.99%
				0.20	96.23%
				0.25	99.67%
		0.04	0.04	0.10	46.34%
				0.15	80.05%
				0.20	96.25%
				0.25	99.67%
		0.05	0.05	0.10	46.39%
				0.15	80.11%
				0.20	96.28%
				0.25	99.68%

7.3 Results

The study was conducted to investigate the gene-gene interaction between HDL associated loci and independent SNPs across the whole genome for HDL levels and cholesterol ratio in Singaporean Chinese population.

7.3.1 Demographic and clinical characteristics of study populations

The main demographic and clinical characteristics of the study subjects are presented in Table 61. In total, 5,272 individuals (1,284 from SCHS controls, 1,889 from

Table 61: Baseline characteristics in different cohorts

	SCES	SCHS	SP2610	SP21m	P
	N = 1889	N = 1284	N = 1146	N = 953	
rs7134375					
CC	1107(58.60%)	767(59.74%)	656(57.24%)	534(56.03%)	
CA	676(35.79%)	437(34.03%)	410(35.78%)	370(38.82%)	0.194
AA	106(5.61%)	80(6.23%)	80(6.98%)	49(5.14%)	
rs266667					
AA	1594(84.38%)	1078(84.09%)	979(85.43%)	769(80.69%)	
AG	280(14.82%)	196(15.29%)	158(13.79%)	181(18.99%)	0.026
GG	15(0.79%)	8(0.62%)	9(0.79%)	3(0.31%)	
rs3764261					
CC	1359(72.13%)	917(71.42%)	811(70.77%)	680(71.35%)	
CA	477(25.32%)	337(26.25%)	303(26.44%)	248(26.02%)	0.980
AA	48(2.55%)	30(2.34%)	32(2.80%)	25(2.62%)	
rs9366874					
AA	872(46.19%)	590(45.95%)	517(45.11%)	436(45.75%)	
AG	833(44.12%)	584(45.48%)	523(45.64%)	421(44.18%)	0.881
GG	183(9.69%)	110(8.57%)	106(9.25%)	96(10.07%)	
Age (year)	58.46±9.54	66.30±7.82	48.67±11.37	46.94±10.34	<0.001
HDL (mmol/L)	1.30±0.40	1.35±0.33	1.45±0.35	1.34±0.36	<0.001
Cholesterol (mmol/L)	5.43±1.04	5.18±0.90	5.21±0.94	5.15±0.87	<0.001
Male	961(51.34%)	816(63.55%)	268(23.39%)	608(63.87%)	<0.001
Hyperlipidemia medication	443(23.45%)	-	105(9.16%)	65(6.83%)	<0.001

SCES, 2,099 from SP2 (SP2610: N = 1146; SP21m: N = 953)) had data available for analysis. As can be seen, HDL levels were similar in SCHS controls and SP21m and it was significantly higher in SP2610 and lower in SCES ($P < 0.001$). Level of cholesterol was just the opposite that it was significantly higher in SCES than in the rest cohorts ($P < 0.001$). The genotype distributions of rs7134375, rs3764261 and rs9366874 were not significantly different across the cohorts (rs7134375: $P = 0.194$; rs3764261: $P = 0.980$; rs9366874: $P = 0.881$) while there was significant difference regarding the genotype distribution of rs266667 ($P = 0.026$). For age, participants were significantly older in SCHS and significantly younger in both SP2610 and

SP21m (P < 0.001). The percentage of males was quite different across cohorts, with SP2610 had significant lower percent (P < 0.001). Table 62 shows the comparison of HDL levels among individuals with and without use of anti-hyperlipidemia medication in different cohorts. Individuals who were not on anti-hyperlipidemia medication treatment had significantly higher HDL levels than those who were on the treatment in all cohorts (SCES: P < 0.001; SP2610: P = 0.016; SP21m: P = 0.021). Thus age, gender and anti-hyperlipidemia medication usage were included in the model as covariates in subsequent analysis.

Table 62: Comparison of HDL levels between individuals with or without anti-cholesterol medication

HDL (mmol/L)	Without Medication	With medication	P value
SCES	1.32 ± 0.40	1.22 ± 0.38	<0.001
SP2610	1.46 ± 0.36	1.37 ± 0.32	0.016
SP21m	1.35 ± 0.37	1.23 ± 0.28	0.021

7.3.2 Main effect and epistasis of SNPs on HDL levels / cholesterol ratio

To investigate whether the association between HDL associated risk loci and HDL level or cholesterol ratio could be modified by gene-gene interaction, epistasis analysis was first performed individually in three independent Chinese cohorts. Pair-wise SNP × SNP interactions between HDL risk loci (N = 47) and independent genome-wide SNPs (N = 74,409) were tested for HDL level and cholesterol ratio.

We observed one gene-gene interaction between rs7134375 and rs266667 for HDL levels (β = 0.286; SE = 0.053; $P_{interaction} = 7.37\times10^{-8}$) and one gene-gene interaction between rs3764261 and rs9366874 (β = -0.216; SE = 0.039; $P_{interaction} = 2.68\times10^{-8}$) for

cholesterol ratio that reached significance level of 10^{-8}. Although both of them did not reach the significant threshold of 1.43×10^{-8} for multiple comparisons, the interaction results were quite consistent across different cohorts and the interaction p-values were very close to the threshold.

Table 63 shows the association between rs7134375 / rs266667 and HDL levels. As can be seen, the minor allele A of rs7134375 would increase HDL levels in most cohorts except in SCHS controls. Although the A allele was reported to significantly increase HDL levels in GWAS catalog [287, 288], the association was not significant in our Singaporean Chinese. The minor allele G of rs266667 was negatively associated with HDL levels in SCES, SCHS controls and SP2610. After meta-analysis, it also could not significantly change the level of HDL in local cohorts.

The result of interaction between rs7134375 and rs266667 on HDL level is presented in Table 64 and Figure 16. As can be seen, a positive interaction was observed between rs7134375 and rs266667 on HDL levels. The results were consistent and there was no heterogeneity among different cohorts. Significant association was found between rs7134375 and HDL level in the heterozygous and minor allele homozygous group of rs266667. The minor allele A of rs7134375 would increase HDL level in these two groups. In addition, the association was stronger in the heterozygous group (P = 0.001) than the minor allele homozygous group (P = 0.005).

Table 63: Main effect between rs7134375/rs266667 and HDL levels

	SCES			SCHS			SP2610			SP21m			Meta-analysis			Heterogeneity	
	β	SE	P	β	SE	P	β	SE	P	β	SE	P	β	SE	P	Q	P_Q
rs7134375	0.017	0.035	0.622	-0.017	0.044	0.696	0.053	0.044	0.234	0.017	0.051	0.734	0.017	0.021	0.409	1.266	0.737
rs266667	-0.059	0.054	0.274	-0.108	0.069	0.117	-0.047	0.073	0.513	0.018	0.075	0.806	-0.053	0.033	0.109	1.550	0.671

Table 64: Interaction between rs7134375 and rs266667 for HDL levels

	SCES			SCHS			SP2610			SP21m			Meta-analysis			Heterogeneity	
	β	SE	P	β	SE	P	β	SE	P	β	SE	P	β	SE	P	Q	P_Q
rs7134375	-0.034	0.038	0.367	-0.061	0.047	0.197	0.010	0.048	0.834	-0.041	0.057	0.473	-0.032	0.023	0.171	1.174	0.759
rs266667	-0.224	0.071	0.002	-0.217	0.084	0.010	-0.204	0.097	0.035	-0.126	0.097	0.196	-0.200	0.043	2.73×10^{-6}	0.739	0.864
Interaction	0.318	0.088	3.16×10^{-4}	0.247	0.110	0.025	0.270	0.112	0.017	0.291	0.126	0.021	0.286	0.053	7.37×10^{-8}	0.280	0.964

Table 65: Main effect between rs3764261/rs9366874 and cholesterol ratio

	SCES			SCHS			SP2610			SP21m			Meta-analysis			Heterogeneity	
	β	SE	P	β	SE	P	β	SE	P	β	SE	P	β	SE	P	Q	P_Q
rs3764261	0.275	0.043	2.01×10^{-10}	0.216	0.053	4.18×10^{-5}	0.138	0.053	0.009	0.236	0.058	5.69×10^{-5}	0.223	0.025	$<1\times10^{-8}$	4.101	0.251
rs9366874	0.011	0.034	0.745	0.039	0.042	0.356	0.012	0.043	0.783	0.017	0.046	0.708	0.019	0.020	0.351	0.310	0.958

Table 66: Interaction between rs3764261 and rs9366874 for cholesterol ratio

	SCES			SCHS			SP2610			SP21m			Meta-analysis			Heterogeneity	
	β	SE	P	β	SE	P	β	SE	P	β	SE	P	β	SE	P	Q	P_Q
rs3764261	0.376	0.058	1.33×10^{-10}	0.420	0.071	5.06×10^{-9}	0.254	0.076	0.001	0.379	0.085	3.39×10^{-6}	0.361	0.035	$<1\times10^{-8}$	2.784	0.426
rs9366874	0.067	0.039	0.089	0.152	0.050	0.002	0.066	0.051	0.192	0.071	0.054	0.188	0.087	0.024	2.54×10^{-4}	2.210	0.530
Interaction	-0.167	0.065	0.010	-0.349	0.083	2.92×10^{-5}	-0.175	0.082	0.033	-0.204	0.087	0.019	-0.216	0.039	2.68×10^{-8}	3.405	0.333

Figure 16: HDL levels depending on the genotypes of rs7134375 and rs266667

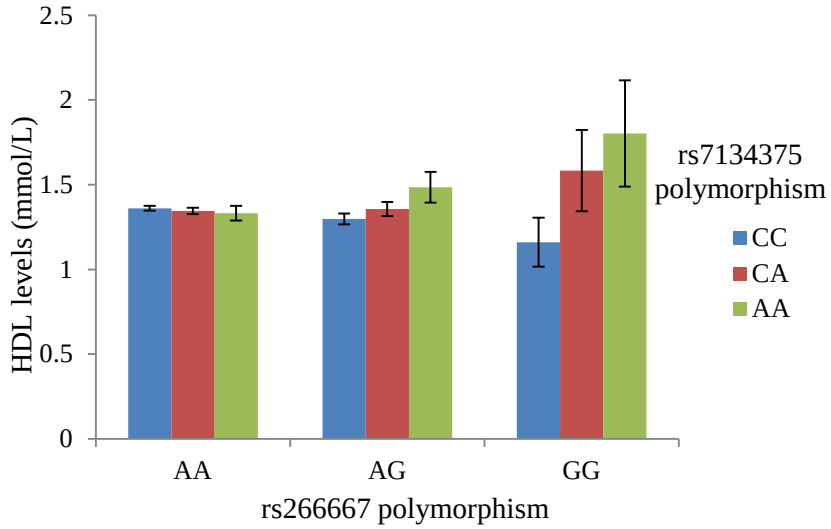
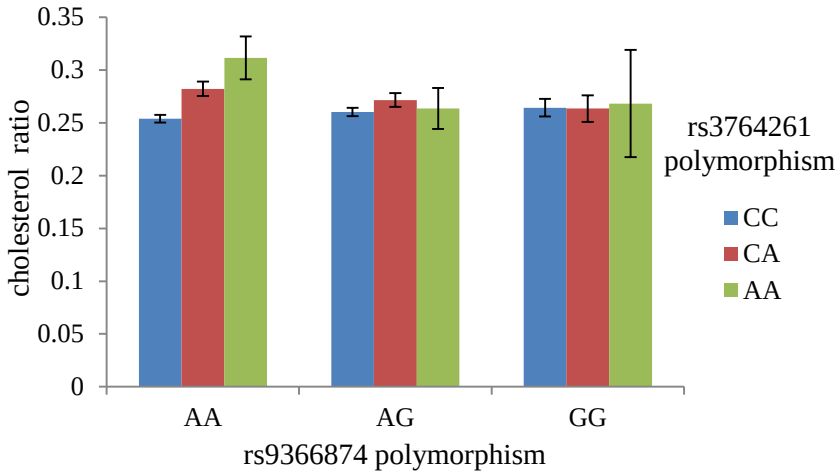


Table 65 shows the association between rs3764261 / rs9366874 and cholesterol ratio in Singaporean Chinese. As shown in Table 65, the minor allele A of rs3764261 would significantly increase cholesterol ratio in all cohorts. After meta-analysis, the association between rs3764261 and cholesterol ratio reached genome-wide significance level (β = 0.223; SE = 0.025; P < 1×10^{-8}). The same allele was previously reported in GWAS catalog to significantly increase HDL cholesterol levels [288-290]. The minor allele G of rs9366874 was positively associated with cholesterol ratio, but the association was not significant after meta-analysis.

The result of interaction between rs3764261 and rs9366874 on cholesterol ratio is presented in Table 66 and Figure 17. As can be seen, a negative interaction was observed between rs3764261 and rs9366874 on cholesterol ratio. The minor allele A of rs3764261 was significantly associated with cholesterol ratio only in the heterozygous and major allele homozygous group of rs9366874. In addition, the

association was much stronger in the major allele homozygous group (P < 0.001) than the heterozygous group (P = 0.001). And the trend of association was much obvious in the homozygous group.

Figure 17: Cholesterol ratio depending on the genotypes of s3764261 and rs9366874



7.4 Discussion

Our study attempted to systematically investigate the interactions between HDL associated risk loci from GWAS catalog and independent SNPs across the genome for HDL levels and cholesterol ratio in Singaporean Chinese cohorts. The analysis was conducted in three independent cohorts individually first and then meta-analyzed with the inverse-variance weighted method. Although none of the interactions remained statistically significant after adjusting for multiple comparisons, the interaction between rs7134375 and rs266667 for HDL levels and the interaction between rs3764261 and rs9366874 for cholesterol ratio reached significance level of 10^{-8}. The interaction results were consistent across different cohorts and the p-values were very close to the threshold. We observed a positive interaction between rs7134375

and rs266667 on HDL levels. It was found that the minor allele A of rs7134375 would significantly increase HDL level in the heterozygous and minor allele homozygous group of rs266667. A negative interaction was observed between rs3764261 and rs9366874 on cholesterol ratio. The minor allele of rs3764261 was significantly associated with cholesterol ratio only in the heterozygous and major allele homozygous group of rs9366874. Meanwhile, the association was much stronger in the major allele homozygous group.

Rs7134375 is a non-coding transcript variant located within *LOC105369688* gene on chromosome 12. The minor allele A of rs7134375 was reported to significantly increase HDL levels [287, 288], but the association could not be replicated in the Singaporean Chinese. To find out the possible mechanism involved, HaploReg (http://www.broadinstitute.org/mammals/haploreg) was used to predict the possible function of rs7134375. The result showed that the allele change of rs7134375, which is located on eleven predicted motif sequences, will likely affect the binding affinity of eleven proteins, such as Jun proto-oncogene, AP-1transcription factor subunit (AP-1), Activating transcription factor 3 (ATF3), CCCTC-binding factor (CTCF), ETS proto-oncogene 1, transcription factor (ETS1), Myogenic differentiation 1 (MYOD1), RAD21 cohesin complex component (RAD21), SIX homeobox 5 (SIX5), Structural maintenance of chromosomes 3 (SMC3), T-box 5 (*TBX5*), TGFB induced factor homeobox 1 (TGIF1) and E1A binding protein p300 (EP300). However, most of the genes coding for these proteins were reported to

associate with different types of cancer. One gene, *TBX5*, was reported to play a role in heart development and specification of limb identity [291, 292]. Rs266667 is an intergenic variant that is also located on chromosome 12. Prediction result from HaploReg suggested that rs266667 might be able to affect the binding affinity of histone deacetylase 2 (HDAC2), a protein playing an important role in transcriptional regulation, cell cycle progression and developmental events. Moreover, histone deacetylases (*HDACs*) was reported to be involved in cardiovascular development and pathology [293]. Since rs7134375 was reported to be significantly associated with HDL level and rs266667 was predicted to affect the binding of the heart disease related HDAC2, it is probable that these two SNPs or their might indeed have a biological interaction with each other to affect HDL.

Rs3764261 is an intergenic SNP on chromosome 16. The minor allele A of rs3764261 was reported to significantly increase HDL levels previously [288-290]. In our study, the same allele was also significantly associated with elevated cholesterol ratio. HaploReg prediction result showed that the allele change of rs3764261, which is located on four predicted motif sequences, will likely affect the binding affinity of four proteins, such as GATA binding protein 3 (GATA3), GLI family zinc finger 1 (GLI1), Heart and neural crest derivatives expressed 1 (HAND1) and Zic family member 1 (Zic1). Among the genes coding for these four proteins, *HAND1* plays a role in cardiac morphogenesis and is the mediator for congenital heart disease [294]. Rs9366874 is an intronic SNP within *LOC340184*

gene on chromosome 6. Prediction result from HaploReg showed that this SNP might be able to affect the binding affinity of RAD21 and sterol O-acyltransferase 1 (SOAT1). *RAD21* is involved in the repair of DNA double-strand breaks but no studies have been published regarding the effect of *RAD21* on lipid levels thus far. SOAT1 catalyzes the formation of fatty acid-cholesterol esters and the mutation on *SOAT1* was reported to be associated with variations in plasma cholesterol and triglyceride levels [295]. Since the minor allele of rs3764261 was reported to significantly increase HDL level and rs9366874 was predicted to affect the binding affinity of SOAT1, the mutation of which was reported to be associated with variations in plasma cholesterol and triglyceride levels, these two SNPs might interact with each other to affect cholesterol ratio.

Although an increasing number of novel polymorphisms associated with lipid traits have been identified through large-scale GWAS, the number of gene-gene interaction studies for plasma lipids is limited. Most of the previous findings were derived from studies involving variants from genes that are involved in lipid metabolism. For example, in 2010, an interaction was found between a novel intergenic polymorphism rs1774572 and TaqIB polymorphism in the *CETP* for HDL cholesterol concentrations [284]. *CETP* plays a central role in the reverse cholesterol transport pathways. The association between TaqIB polymorphism and HDL levels has been firmly existed in several populations. We also included some genetic variants from *CETP* in our study, but no significant interactions were observed. In the same year,

interaction between the upstream stimulatory factor (*USF1*) and *APOA5* on lipid levels and atherosclerosis was reported in another study [296]. *USF1* regulates the expression of multiple genes involved in lipid metabolism [297] and *APOA5* is involved in TG metabolism [298, 299]. Genetic variants on *APOA5* were also included in set one. However, no significant interactions were observed in current study. Investigating gene-gene interactions by choosing SNPs within genes that are involved in lipid metabolic pathways may be more likely to detect the interactions and explain the possible mechanisms involved. However, selecting SNPs by the candidate gene approach will also mean missing out yet to be identified genetic variants that associated with plasma lipid levels. Our study has systematically investigated the interactions between HDL associated risk loci from GWAS catalog and independent SNPs across the genome for HDL levels and cholesterol ratio in Singaporean Chinese cohorts. Although none of the interactions remained statistically significant after adjusting for multiple comparison, we found two interactions that are consistent across different cohorts and the p-values were very close to the threshold. Additional Chinese cohorts are needed to further confirm our findings.

In summary, we observed the interaction between rs7134375 and rs266667 for HDL levels and the interaction between rs3764261 and rs9366874 for cholesterol ratio that reached significance level of 10^{-8} in Singaporean Chinese, which are very close but has not reached the significance level after adjustment for multiple comparisons.

Our study sheds light on the possible gene-gene interactions for lipid traits, which could partially make up for the ‘missing heritability’ for complex diseases.

Chapter 8: Conclusion

8.1 Main findings

This dissertation is focused on the genetic epidemiological investigations of CAD and its related traits.

The rapid development and the reduction in the cost currently made GWAS a powerful tool to provide a valuable first insight into genetic architecture or candidate loci of CAD and its related traits for subsequent validation and biological analysis [23].

In 2011, an intronic SNP rs6903956 on chromosome 6p24.1 within the *C6orf105* region was found to be associated with CAD risk in a GWAS conducted in a Han Chinese population. It is found that the mRNA expression of *C6orf105* was significantly lower in the minor allele homozygous (AA) and heterozygous (AG) groups compared to the major allele homozygous (GG) group [46]. Later in the same year, *C6orf105* region was found to code for a novel transmembrane protein. This novel transmembrane protein could regulate mRNA expression, cellular distribution and anticoagulant activity of *TFPI* gene, both under native condition and in response to androgen. As such, it has been named androgen-dependent *TFPI* regulating protein (*ADTRP*). The association between rs6903956 and CAD risk has been replicated in several independent Chinese cohorts [47, 107] as well as in the Japanese but differing in the risk allele [48]. Notably, the association has not been

found in the European populations [89]. Our group had reported previously that the minor A allele of rs6903956 significantly increased CAD risk in the Singaporean Chinese and that association was not explained by plasma lipid levels [47]. Besides lipid levels, coagulative factors also played a central role in advancing atherosclerosis as well as leading to CAD [49-51]. High levels of FVII and fibrinogen have been found to be significantly associated with increased risk of coronary events [52]. We conducted analysis both in Chinese adults and neonates to investigate whether there is any association between rs6903956 and coagulation factors. No significant association was observed in both adult and neonatal cohorts and thus the genetic variant was not associated with either FVII or fibrinogen level in the Singaporean Chinese (Study I).

To date, GWAS have identified many SNPs that are associated with CHD and its related risk factor traits. The identification of these SNPs made it possible to utilize genetic information to predict individual risk of getting CHD. Numerous phenotype based equations for predicting risk of 'hard' CHD are currently available, such as the Framingham Risk Equation, SCORE and QRISK [152, 155, 157, 229, 230]. The most popular model ATPIII [231] performed well in multiple cohorts with or without model recalibration [160, 164, 165, 233]. However, there were still a proportion of individuals with few risk factors and predicted to be at low risk of developing disease were actually CHD patients [234, 235]. Therefore, we believed that including genetic information into phenotype based equations could provide additional

accuracy. We constructed and tested four GRS that contains multiple SNPs selecting by two different criteria. All the GRS was significantly associated with incident 'hard' CHD after adjustment for traditional risk factors (age, TC, SBP, HDL, cigarette smoking and anti-hypertension medication usage) and recent ones such as hsCRP and creatinine. The inclusion of the GRS into the phenotypic risk models led to the improvement in discrimination and risk classification in most situations. The performance of the GRS containing larger number of SNPs (reported to be associated with CHD or its related traits) was better than the GRS including only a small set of SNPs (reported to be associated with CHD or MI) in terms of their effect sizes, model discrimination and risk classifications. It is also found that the performance of the GRS containing SNPs filtered by the Cox proportional hazards models with adjustments for age and gender was much better than the GRS containing SNPs robustly associated with CHD and its risk factors. Although the extent of improvement of c-statistics was smaller in women than those in men when compared to the same base model using the same GRS, the addition of GRS to all models resulted in better c-statistics in women, especially the 51-SNPs GRS, which attained c-statistics all above 0.80 (Study II).

As with all complex disease traits, it is known that gene-gene and gene-environment interactions also play a role in determining the outcome of CAD and its related risk factors in addition to the direct effect of genetic and lifestyle factors. The last component of the dissertation included gene-diet interaction study for BMI and

gene-gene interaction study for plasma lipid, HDL and cholesterol ratio.

Being overweight or obese will lead to adverse metabolic effects on blood pressure and lipid levels. Individuals who are overweight or obese will have higher risk for various diseases, including CHD [8, 30]. Recent GWAS have identified 97 BMI associated SNPs. These obesity risk SNPs are generally transferable between ethnic groups. However, differences exist in dietary patterns between ethnic groups and whether dietary intake of various nutrients can modify obesity associations at these recently identified risk loci is not well known. We first tested the association between various dietary components (total calories, cholesterol, %protein, starch, fiber, %fat, %SFA, %MFA, %PFA and %carbohydrate) and BMI. Only total calories intake was significantly associated with increased BMI after adjusting for multiple comparisons. We also replicated the association between these reported BMI risk loci and BMI levels in our Singaporean Chinese population. It is found that most of the BMI susceptibility loci, although not statistically significant, showed directionally consistent association with BMI as reported previously [251]. We then investigated whether these BMI associated risk loci could affect various dietary intake and found the reported BMI risk allele G of rs6804842 on *RARB* gene would increase intake of total calories. Finally, we checked whether dietary intake can modify obesity associations at these recently identified risk loci. Interaction analyses results revealed nominal significance for %fat × rs205262 (*C6orf106*), cholesterol × rs4740619 (*CCDC171*) and %SFA × rs11126666 (*KCNK3*) on BMI

(Study III).

Besides BMI, HDL is also a risk factor for CAD risk. Low concentration of HDL is strongly associated with increased risk of cardiovascular disease [40, 41] and every 1 mg/dl decrease in HDL level will lead to a 6% increase in cardiovascular risk [42]. GWAS has identified hundreds of SNPs associated with plasma lipid levels thus far [78]. We thus explored the interactions between HDL associated risk loci from GWAS catalog [78] and independent SNPs across the genome for HDL levels and cholesterol ratio in Singaporean Chinese cohorts. Although none of the interaction results remained statistically significant after Bonferroni correction, interaction between rs7134375 and rs266667 for HDL levels and the interaction between rs3764261 and rs9366874 for cholesterol ratio reached significance level of 10^{-8}. In addition, the interaction results were quite consistent across different cohorts and the p-values were very close to the threshold (Study IV).

8.2 Limitation and future work

Our previous study reported that the association between rs6903956 and CAD risk was not explained by plasma lipid levels [47]. In Study I, we further investigated and found that the genetic variant was not associated with FVII and fibrinogen. The effect of the rs6903956 on CAD risk might therefore be mediated through other coagulation factors, such as TF or TFPI. The influence might be more upstream in the coagulation cascade since ADTRP is known to regulate the levels of TFPI.

Additional investigation is needed to uncover the actual mechanisms involved.

In genetic epidemiological study, one tries to identify the association of risk factors with diseases and quantitative traits. In addition, one also tries to unravel the causal relationship between genes and the outcomes. For Mendelian traits, the genetic variant is usually a sufficient cause for the outcome. In other words, the individuals will have the disease as long as the mutation exists. While for complex diseases the genetic variant is a probabilistic cause which can increase the likelihood of the outcome as well as in altering the level of quantitative traits, [300]. The probabilistic cause is neither necessary nor sufficient. Thus it is much more complicated to prove causal relationship in complex diseases and quantitative traits than Mendelian traits [301]. GWAS is a popular and powerful tool to identify susceptibility loci for various diseases and quantitative traits. However, the relationship identified by GWAS between SNPs and various outcomes can only be established as association and not causation. GWAS is unable to identify the causative or susceptibility genes involved in complex diseases and quantitative traits. When an association between polymorphism and a disease or quantitative trait is identified by GWAS, it could be due to one of the following reasons: (1) true causation; (2) false positive findings; (3) the identified polymorphism is in LD with the true causative allele; (4) systematic bias. To prove an association as the causation, other evidence is needed. In 1965, a list of guidelines for epidemiological causation in environmental and occupational medicine were raised by Sir Austin

Bradford Hill [302]. Replication is one of the best ways to prove the validity of the result thus to infer the possible causation (consistency and unbiasedness of association). In Study III, although we observed nominal significance for %fat × rs205262 (*C6orf106*), cholesterol × rs4740619 (*CCDC171*) and %SFA × rs11126666 (*KCNK3*) on BMI, additional cohorts are necessary to replicate and further confirm the results. In addition, we could check whether the association we observe is biological plausibility. In Study III and Study IV, we used HaploReg, a tool for exploring the annotations of the non-coding genome at variants on haplotype blocks to find out the possible biological plausibility. However, the results provided by HaploReg are just a prediction for the gene function. Experimental evidence is still needed to consolidate the causal relationship.

Sample size is an extremely important element in GWAS and population studies. In Study II, we did not split our dataset into a separate training and validation dataset due to relatively small sample size. We are mindful that there could be over-fitting with our results and hence have attempted to minimize this by performing internal cross-validation when reporting the results. External replication in independent cohorts is ultimately needed to further validate the predictiveness of the GRS. Multiple testing is another issue in GWAS [129]. In Study IV, we used the candidate gene approach to select the first set of SNPs and only included SNPs that have been genotyped so as to reduce the number of multiple comparisons. Although interaction between rs7134375 and rs266667 for HDL levels and the interaction

between rs3764261 and rs9366874 for cholesterol ratio reached significance level of 10^{-8}, which is very close to the threshold, both of the interaction results could not attain statistical significance after correction for multiple testing. Additional Chinese cohorts are therefore needed to further confirm our findings.

Since the genotyping arrays used for GWAS are based on tagging SNPs, it does not directly genotype all genetic variants in the genome. For SNPs without genotype information, imputation of the genotypes based on a reference panel can be used to boost the coverage of genomic variation. In both Study II and Study III, genotype calls were based on International HapMap Project [123] East-Asian samples that were derived from Han Chinese from Beijing (CHB) and the Japanese in Tokyo (JPT). To further increase the number of SNPs that can be included in the study, the 1000 Genome Project [124] could be used as a imputation reference panel. This was not available at the time of our analysis but can be included in the future.

With the identification and validation of the gene-gene and gene-environment interaction for CAD and its related traits in addition to BMI and HDL, the incorporation of interaction terms into the risk prediction models is expected to further improve prediction accuracy. Additionally, although GWAS is a powerful tool to identify susceptibility loci, individually the SNPs uncovered by GWAS only explain a small proportion of the variance / heritability of CHD and its related traits. Additional studies to identify more common variants and other variants not

effectively captured by GWAS using other methods, such as rare variants and structural variants, and include them in future models may further improve risk prediction accuracy.

Traditional case-control studies usually identify disease-causing genes by comparing a group of diseased individuals with a group of healthy individuals. In recent decades, there is an argument stating that sequencing the genomes of very healthy old people (super controls) to identify the protective rare gene variants can offer better insights into mechanisms [303]. In contrast, we could also sequence the genomes of early onset diseased individuals by exome sequencing to identify the risk rare gene mutations [304-306].

8.3 Summary

In conclusion, this dissertation has demonstrated that the genetic variant rs6903956 within the *ADTRP* gene is not associated with the plasma coagulation factors, FVII and fibrinogen. It is also found that the inclusion of genetic information into phenotype based risk prediction equations could further improve prediction accuracy and model performances. The identification of the gene-diet interaction for BMI and gene-gene interaction for HDL could deepen the understanding of complex etiology of CAD and its related traits. It also provides a possible way to further improve risk prediction model for CAD. Replication and further experimental studies will be necessary to uncover the mechanisms involved.

List of Publications

1. **Chang, X.**, A. Salim, R. Dorajoo, Y. Han, C.-C. Khor, R. M. van Dam, J.-M. Yuan, W.-P. Koh, J. Liu and D. Y. Goh (2017). "Utility of genetic and non-genetic risk factors in predicting coronary heart disease in Singaporean Chinese." *European Journal of Preventive Cardiology* **24**(2): 153-160.
2. **Chang, X.**, H.-L. Chin, S.-C. Quek, D. Y. Goh, R. Dorajoo, Y. Friedlander and C.-K. Heng (2017). "The genetic variation rs6903956 in the novel androgen-dependent tissue factor pathway inhibitor regulating protein (ADTRP) gene is not associated with levels of plasma coagulation factors in the Singaporean Chinese." *Thrombosis Journal* **15**(1): 1.
3. Han, Y., R. Dorajoo, T. Ke, B. Ayala, **X. Chang**, C.-C. Khor, R. M. van Dam, J.-M. Yuan, W.-P. Koh and J. Liu (2015). "Interaction effects between Paraoxonase 1 variants and cigarette smoking on risk of coronary heart disease in a Singaporean Chinese population." *Atherosclerosis* **240**(1): 40-45.
4. Dorajoo, R., Y. Sun, Y. Han, T. Ke, A. Burger, **X. Chang**, H. Q. Low, W. Guan, R. N. Lemaitre and C.-C. Khor (2015). "A genome-wide association study of n-3 and n-6 plasma fatty acids in a Singaporean Chinese population." *Genes & nutrition* **10**(6): 1-11.

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